# THE KIDNEY

*Medical and Surgical Diseases*



*"To connect accurate and faithful observations after death with symptoms displayed during life must be in some degree to forward the objects of our noble arts"*

From the preface to "Reports of Medical Cases Selected With a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy," by Richard Bright (Published by Longman, Rees, Orme, Brown and Green, London, 1827)

# THE KIDNEY

*MEDICAL AND SURGICAL DISEASES*

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*1115 Illustrations*

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# Contents

# Introduction

In recent years there has been a resurgence of interest in the kidney stimulated in large measure by three factors: (1) an increased and refined awareness of the vital role of the kidney in the maintenance of electrolytic and fluid balances, (2) new methods of investigation of renal function, and (3) a rise in incidence of certain diseases, such as hemoglobinuric nephrosis and hypertension It would seem mandatory when advances or, at least, changes in concepts take place in the fields of clinical medicine or physiology that they be matched by a discerning review of the related pathology Conversely, of course, the discoveries in the field of morbid anatomy—and let us make no mistake, the reported sterility of this science is somewhat of an exaggeration—should open new avenues of physiologic investigation, or perhaps widen the old ones For various reasons—reasons that, as a rule, are by-products of the wasteful separation of studies of structure as opposed to function—there have been long lags in both directions

At this time, perhaps no other organ lends itself to as close a clinicopathologic correlation as does the kidney This is so because disorders of renal functions are reflected by a great variety of physicochemical changes which can be measured or calculated with relative ease and accuracy Moreover, in many instances, the basis for the physiologic derangements is histologically visible, and there to be properly interpreted Undoubtedly, revised investigative methods will, in the future, yield other histologic facts However, the principal difficulty to date is not that the pathologic changes are beyond the range of the microscope, but that there has been accumulated in the technical journals, in the texts and in the classroom a number of discrepancies concerning the histologic as well as the physiologic changes in the kidney Into this category of contentious pathology fall diabetic glomerulosclerosis, hemoglobinuric nephrosis, osmotic nephrosis, cholemic nephrosis, myeloma nephrosis, generalized arteriolocapillary "thrombosis," focal endocarditic ("embolic") glomerulonephritis, amyloidosis, disseminated lupus erythematosus, chronic nephrotic glomerulonephritis ("lipoid nephrosis"), "renal rickets," bilateral cortical necrosis, the renal lesions of the toxemias of pregnancy and a great many other conditions

One reason for the discordant clinicopathologic correlation is that there is an inadequate qualitative *and especially quantitative* check of investigative physiologic tests with dynamic morphologic data. There are very many examples of renal dysfunction that have been speciously explained away with attractive, easily retained but obstructive histologic clichés, such as "diffuse vascular disease," "tubular amyloidosis," "calcification of tubules," "hydropic" or "cloudy swelling," "necrotic tubules," "interstitial edema," and "blockage by casts " The point about the misuse of these diagnoses is not necessarily their accuracy, but that however sparse or focal such lesions may be, they are often blamed for the entire renal disturbance

The pathologist himself must bear much of the blame for having permitted a hyperbolic adaptation of the effective histologic data However, the deficiency is not entirely the pathologist's, the clinical physiologists must take a modicum of the responsibility For one thing, the facile morphologic reconstructions of renal diseases based on clearance studies warrant re-examination No one need offer an apologia for the past and ultimate usefulness and brilliance of investigations by clearance methods. However, it would be a disservice to fail to declare that, in many instances, interpretations of clearances represent a subjugation of a complicated histologic panorama to impres-

sive, meticulously quantitated, but dubiously applied physiologic data The situation involves a rather astonishing paradox. On the one hand, physiologists eagerly report elaborate combinations of clearance tests to a decimal place On the other hand, they feel justified in attributing acidosis, for example, to calcification of the distal convoluted tubules without attempting to determine if one, a few, or all of the nephrons are involved Another instance of the too ready conversion of the results of physiologic tests into broad principles is the explanation of the mechanism of the anuria of hemoglobinuric nephrosis. The anuria is tenuously ascribed to necrosis of tubular epithelium in the lower portions of the nephrons, resulting in complete back diffusion of glomerular filtrate. The fact is that the extent of the necrosis in hemoglobinuric nephrosis with anuria is commonly very meager. These are just two of numerous examples indicative of the excessive divergence between histologic fact and physiologic evaluation No less in need of reorientation is a cluster of ideas derived from questionable concepts of certain structural changes, some of which were indicated in a previous paragraph Such a physiologic and pathologic analysis is herein attempted

In the same spirit of trying constructively to uncloak some home truths, there is this to be said to pathologists: it is plain* that many pathologists feel that their function with regard to the histologic analysis of the kidney should be limited to the routine brute description of the pathologic changes Specific clinicopathologic interpretation, they feel, is the job of the clinician Actually there is an appreciable number of diseases that leave their diagnostic label in the kidney, a label that is clearly detectable with the microscope Sometimes the label is a lf-sufficient, specific histologic change; at r times, the definitive histologic picture is de up of a composite of changes, no one of which may establish the diagnosis until all are evaluated together. This situation, in principle, applies not only to the pathologic diagnosis of every organ of the body, but certainly also to the field of clinical diagnosis as well. Demonstration of the proof of the validity of this thesis in renal pathology is one of the chief objectives of this book. However, the practice of this thesis certainly does not preclude the use of all accessible clinical and physiologic data by pathologists Surely it is incumbent on the pathologist to try to integrate these data with the pertinent physiologic disorders they reflect, and thereby to give his colleagues a working interpretation of pathologic changes. The pathologist is in a pivotal position to make this integration, to fail to do so is to disregard the third dimension of the science of pathology.

With these thoughts in mind and with the added belief that the kaleidoscopic accumulation of new facts and hypotheses requires a critically purposeful inventory, this atlas and text of renal diseases was compiled. Emphasis has been placed on pathology—we trust the emphasis is on the *dynamic* rather than static, oppressively descriptive pathology. The stress is naturally so directed because the author is a pathologist, however, it happens also to be his conviction that, by this approach, proportionately *relieved with principles of clinical physiology*, the book—if it has any quality—should be of some use not only to pathologists, but particularly to urologists, internists, investigators, and undergraduate students. Toward this end, the photographs and text have been arranged in a pedagogic sequence intended for ease and clarity of presentation of individual diseases and of their differential aspects Guided by the knowledge that the reader is at least as perceptive as the author—a rule worthy of general consideration—the unresolved problems are, for the most part, presented as if they *are* unresolved, rather than as if they are happily and dramatically settled. It would seem axiomatic that when there are great gaps in the evidence, it is unwise to present a situation in a lavishly wrapped package leaving the disappointing contents to be discovered in the future. On the other hand, tabulated items gathered comprehensively from the literature lose much of their usefulness unless they have been judiciously evaluated and synthesized. In this proc-

* See Proceedings of the 13th Seminar of the American Society of Clinical Pathologists, by Balduin Lucké and Arthur C Allen, published by the Army Institute of Pathology, 1947.

ess of clarification, there lurks continually the hazard of oversimplification or of misjudgment. If such errors have occurred—and undoubtedly some of the conclusions are likely to provoke sharp differences of opinion—then it is hoped that they will not be attributed to a failure to hunt earnestly for the truth.

Approximately one-fifth of the photographs and a much smaller proportion of the text deal with neoplasms of the kidney Reference to the section on tumors of the kidney is made separately because the scope of the problem is, in general, of a different order from that of other diseases of the kidney One day this scope will be broadened when we have become equipped with the biochemical secrets of renal carcinogenesis which must expose mechanisms of prophylaxis and therapy of a corresponding biochemical character. Currently, however, the practical problems of renal neoplasms are similar to those of other organs, namely, early diagnosis, adequate obliterative treatment, and prognosis Attention has, therefore, been concentrated on the wide range of variation, particularly in histology, of the different tumors, and on their mode of behavior

Much of the experience on which this survey is based was accumulated over the past fifteen years by the study of fairly extensive material during the author's association with various large institutions In addition, many individuals have generously permitted a first-hand study of their special cases for which acknowledgment within the text is an inadequate expression of appreciation It is felt, however, that the use made of these contributions by pathologists, clinicians, and especially students, will be a source of some satisfaction to the donors

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# 1. Embryology

THE embryology of the kidney is a rather vivid example of the principle of phylogenetic recapitulation In its maturation, the kidney of man passes through three stages of development· (1) the pronephros, (2) the mesonephros and (3) the metanephros The pronephros is functional as an adult organ only in the Amphioxus and in certain lampreys The mesonephros replaces the pronephros to become the permanent kidney of fish and amphibians In reptiles, birds and mammals, the metanephros is evolved from the pronephros and mesonephros to become the adult kidney In the latter groups, the three kidneys develop successively, one into the other, with some overlapping in the time of appearance

In the ontogenetic development of most of the viscera (e g , the pancreas, the liver, the spleen) there is normally a progressive and direct evolution of the mature organ from its early fetal anlage In the case of the kidney, the final organ or metanephros appears to develop in the most circuitous, recondite, and economically unsound fashion from the seemingly cumbersome stages of the pronephros and mesonephros The final location and construction of the kidney bears so little gross resemblance to its anlage that it might even suggest to some a providential lapse of planning It is hardly likely that the planning has been defective It is more reasonable to assume not only that the excretory apparatus present at a given stage is the most efficient for that stage, but also that it is essential for the completion of the succeeding phase Of interest in this regard is the fact that interference with the development of the pronephros and mesonephros, (e g, cutting the pronephric duct) effects the maturation of the intermediate or final kidney Precisely by what biochemical mechanism the pronephros "induces" the organization of the mesonephros and metanephros is a problem for the future The chief point is that apparently purposeless fetal structures may be assumed to have functions linked with the remainder of the embryonic economy although, at times, such functions may escape our understanding

For reasons to be mentioned, it is of considerable conceptional significance that all three forms of kidneys have much in common in their unit of structure, even though they differ considerably in the pattern of the final tubular and vascular arrangements The tubules in all three arise from the mesoderm of the intermediate cell mass (or its extension, the nephrogenic cord) which lies between the somatic and splanchnic layers of the mesoderm enveloping the celom In each of these stages, the excretory apparatus includes glomeruli, tubules and a main duct Moreover, it is remarkable to note the essential morphologic identity of the glomerulus of the pronephros, mesonephros and metanephros (plates 1, 3 and 4)

*Pronephros*

The pronephros is the first and most cranially situated of the three kidneys It consists of about seven pairs of segmentally arranged tubules formed as dorsolateral sprouts from the nephrotomes of the 7th to 14th mesodermal segments One end of each tubule, a ciliated *nephrostome*, drains the celomic cavity, the other empties into a common excretory or *pronephric* duct which is formed from the union of the ventral portions of the primitive tubules and empties into the *cloaca* (plate 2) The waste products which reach the celomic cavity represent the filtrates from a tuft of capillaries, or glomerulus, formed from an offshoot of the aorta This cluster of capillaries invaginates the celomic mesothelium to form a glomerular hillock This glomerulus has only a thin splanchnopleural layer separating it from the celomic cavity In other words, it does not have the Bowman's space, "parietal epithelium" or Bowman's capsule as do the mesonephric and adult glomeruli, but, otherwise, there is close structural resemblance, as

mentioned However, the pronephric glomerulus lies adjacent to its appertaining, cuplike ciliated nephrostome, so that wastes from the blood filtered into the celomic cavity are readily sucked through the nephrostome into the pronephric tubule and drained into the common pronephric duct The pronephric duct links the series of pronephric units (plate 2B).

Although the pronephric tubules themselves do not develop distal to the 14th somite, their collecting, or pronephric duct does grow far beyond this level caudally until it reaches and *perforates the cloaca. The pronephros begins* to appear in 2-3 mm embryos of nine somites (about the twentieth day) and is completed at about the stage of 23 somites (4-5 mm embryos, about 24 days) The pronephric duct reaches the cloaca shortly after this period The pronephric duct then serves as the excretory or mesonephric duct for the following set of kidneys, the mesonephros (plate 2 D, F)

*Mesonephros*

The *mesonephros*, or *wolffian body*, begins to appear at the level of the 14th somite in embryos about 24 days old The tubules extend cephalically a few somites to overlap the pronephric tubules and reach their caudal limit at the second lumbar segment (26th somite) when the embryo is 7-8 mm in length (five weeks) The mesonephros and the pronephros *arise from the same general source*, the region of the nephrotome, or intermediate *mesoderm, which appears as a continuous* bridge between somites and is therefore known as the *nephrogenic cord* The mesonephric tu*bules which arise from the nephrogenic cord* do not tend to correspond to body segmentation, two or three, or as many as nine, may occupy the distance of one somite.

The nephrogenic masses hollow out into S-shaped tubules *One end of the tubule* communicates with the original pronephric duct, now the *mesonephric* or *wolffian excretory duct*; the other end does not open into the celomic cavity by way of a nephrostome as *does the pronephros, but, instead, cups itself* about the knot of blood vessels, or glomerulus, which, together with the invaginated tubular capsule, constitute the *mesonephric corpuscle.* The blood vessels of the glomeruli, as in the pronephros, arise from arterial twigs coming ventrolaterally off the aorta. The glomerular efferent vessels break up into a plexus of peritubular anastomosing venous sinusoids which empty into the posterior subcardinal veins and comprise a renal portal system. At this stage *the mesonephric tubule is differentiated into a* thicker proximal secretory segment and a thinner collecting segment which empties into the mesonephric duct.

The enlarging line of mesonephric tubules *bulges ventrally into the celom* so as to produce a longitudinal *urogenital ridge* for a distance of 15 somites on each side of the dorsal mesentery Very shortly this fold becomes subdivided into lateral mesonephric and medial genital ridges.

After the fourth week, the cranial mesonephric tubules undergo degeneration as new tubules are formed caudally At the end of the eighth week, the upper five-sixths of the mesonephric body of tubules are lost, having undergone degeneration and transformation into the diaphragmatic ligament of the mesonephros Some of the remaining tubules appear to give rise to others by budding. A maximum of about 80 pairs of tubules are formed and, of these, about 34 pairs persist to nine weeks At this time, only about 17 pairs of tubules are functional, and in another week, they all become vestigial, although degeneration is not complete until the end of the fourth month.

*Metanephros*

The *metanephros, or permanent kidney* of humans, arises from two different portions of the mesonephros. (1) the ureter, renal pelvis, and collecting tubules come from the distal end of the mesonephric duct, and (2) the cortex, *with the exception of the collecting* tubules (medullary rays) included in the cortex, is derived from the caudal end of the nephrogenic mesodermal mass (plate 2D).

Just prior to its entrance into the cloaca, *the mesonephric duct bends sharply* This angle marks the site at which the metanephric hillock, or *ureteral bud* first appears, about the fourth week (5 mm embryos) In invaginating,



FIG A *Mesonephros of a 9 mm human embryo showing well developed glomeruli and appertaining tubules* The degree of development of the glomeruli (fig B) is remarkable for its approximation of the adult kidney

FIG B *High magnification of left mesonephros of* figure A These glomeruli are indistinguishable from those of the metanephric or permanent kidney

FIG C *Kidney of a 1 4 cm human embryo showing* extension of ureteral bud into the peripheral metanephrogenic tissue which is converted into glomeruli and portions of the nephron

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(The histologic slides, from which the photomicrographs in this book were made, were stained with hematoxylin eosin, unless otherwise indicated )

the bud cups out the caudal tip of the nephrogenic cord, which forms a closely investing cap over the primordium of the inner, or pelvic, portion of the adult kidney The site of attachment of the diverticulum with its intimately linked nephrogenic mass becomes elongated into a tube to form, eventually, the ureter At the same time, the primitive kidney, or, more particularly, the caudal end of the *nephrogenic mass* separates from the remainder of the more proximal mesonephric tissue and, at nine weeks, comes to be at its final position retroperitoneally at the level of the mid-lumbar segment The pelvis then sprouts numerous generations of calyces and tubules into its closely applied investiture of nephrogenic tissue until, at the time of birth, there is a maximum of 20 branchings Most of the ramifications of the pelvic off-shoots are aggregated into the medulla in the form of pyramids, a few of the collecting tubules string out into the cortex where they are known as the *medullary rays* The interdigitation between medullary and cortical primordia is further secured by the dipping of fingers of cortex (*columns of Bertin*) between the inverted medullary pyramids Each pyramid and its associated cortical tissue comprise a geographic unit that is reflected on the capsular surface of the embryonic kidney by indentations known as *fetal lobulations* These interlobular grooves, which characterize the adult kidney of reptiles, birds and some mammals, for the most part disappear in early infancy and childhood although residual traces of them are common in adults (plate 7)

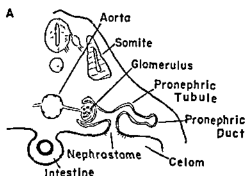
*Linkage of Proximal and Distal Nephrons*

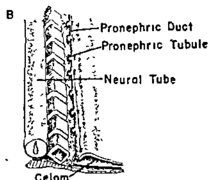
It has been generally assumed that the distal portion of the nephron, arising from the metanephric diverticulum, and the proximal portion, arising from the nephrogenic mesodermic cap, represent the pari passu development of the two separate components of the nephron which subsequently unite It has been further assumed by many observers that the failure of the two units to unite is the dysembryogenic basis for the polycystic kidney, the cysts resumably arising from functional but closed proximal portions of the nephron However, detailed histologic study suggests an opposing concept which might be called the "unitary theory" (plate 6).

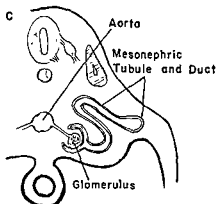
*Unitary Theory*

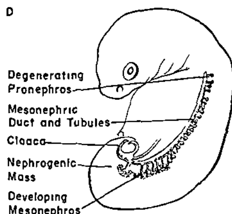
A study of serial sections of the various stages of fetal kidneys leads to a somewhat different impression, namely, that the metanephric diverticulum does not abruptly cease its branching with formation of collecting and distal tubules, but ramifies into the nephrogenic tissue, the active primordial, multipotent cells of which are progressively added as epithelium corresponding to the cells of the advancing tubular buds until the entire length of the tubule is formed (plates 3, 4, 5 and 6). In other words, it is not as if two separate segments of contorted tubules had their two individual lumens made one after their respective blind ends were somehow opened and joined, it is rather that a single lumen becomes elongated by the accretion to its tubular lining of cells from the peripheral nephrogenic mass made receptive to canalization by the influence of organizers The dynamics of this process can hardly be adequately documented merely with several photomicrographs but perhaps the general thesis can be gathered from plates 1 through 6 If an occlusion were to occur in some segment of the tubule, the still functioning portion of the nephron proximal to the obstruction would become dilated with fluid The precise mechanism of the occlusion in congenital polycystic kidneys remains to be elucidated but intratubular atresia or obstruction due to extratubular fibrosis are the two possibilities In view of the common association of polycystic kidneys with cysts of the liver and pancreas, it is not unreasonable to assume that a similar developmental fault might be responsible for the cysts in each of these organs, rather than the failure of two separate units to be joined An obstructive mechanism through atresia or periductal fibrosis has in its favor a common application to these several organs

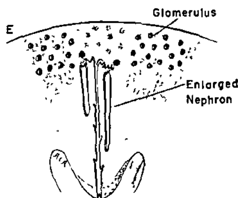
In additional support of this unitary theory of origin of the renal tubule is the basically similar mode of development of the pronephric and mesonephric tubules (as well as their glo-



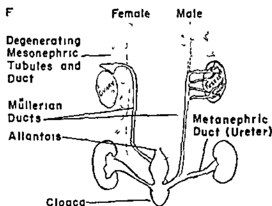




FIG A *Pronephros* of human kidney in section

FIG C *Mesonephros in section* (5 mm human embryo)

FIG E *Kidney of newborn* showing two nephrons diagrammatically enlarged

FIG B *Pronephros* (after Felix and Turland)

FIG D Relationship of pronephros, mesonephros and metanephros in human embryo

FIG F *Relationship of genital to urinary systems*, indicating the embryogenesis of vestigial structures (After Patten)







FIG A *Kidney from 4 cm human fetus* showing ramifications of ureteral bud to the germinal tissue at the rim Newly formed or forming glomeruli are near the surface or at the analogous location, namely, the site of lobular fissures

FIG B *Kidney from 5 cm human fetus* The peripheral extension of a ramification of a ureteral bud is illustrated The glomerulus and proximal nephron are formed *not* as a separate unit which subsequently joins the ureteral ramification but rather by the tubular outgrowth of the latter into the highly active and multipotent subcapsular cells




FIG A *Kidney from 6 cm human fetus* illustrating the formation of the proximal portion of the nephron The subcapsular undifferentiated cells which resemble stromal cells are converted into the epithelium of the glomerulus and proximal tubules

FIG B *Kidney from 6 7 cm human fetus* Various stages in the formation of glomeruli from the coiled distal ramification of the ureteral bud are illustrated




FIG A *Kidney from a 9 cm human embryo* The continuous coiling of the ureteral tubular digitation into the preglomerular and proximal tubular structure is illustrated This field indicates the initial invagination of the distal end of the coil by capillaries in the process of glomerular formation (arrow)

FIG B *Kidney from a full term human fetus* showing early stages in glomerular formation in the subcapsular region This photomicrograph illustrates that the formation of glomeruli may not be completed at term, but may extend for several months afterward

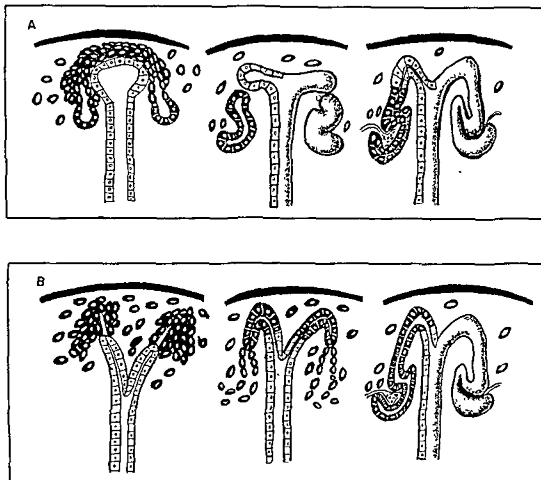



FIG A *The current concept* of the development of the nephron is that the secretory or proximal and distal portions of the nephron develop as separate histologic units after which they normally unite to form the complete nephron Figure A represents successive stages in this development

[illegible]

ureteral bud on the metanephrogenic mass which permits growth of the convoluted nephron by progressively adding these converted epithelial cells as blocks to the pre existing epithelial cells of the advancing tubule In other words, it does not appear that the proximal and distal portions of the nephron grow separately with final union of their separate lumens, only a single advancing lumen appears to exist in the developing nephron rather than two distinct lumens

meruli, incidentally). Although these tubules are not as differentiated in their functions and development as are those of the final kidney, nevertheless, they are not simple urinary conduits but carry on complicated resorptive as well as aqueductal functions. And yet, no one thinks of postulating that the glomerulus and its adjacent segment of nephron is cemented to the distal portion to complete the pronephric or mesonephric nephron The comparison is not hyperbolic; after all, the nephrogenic cap into which the metanephric diverticulum ramifies is merely the most caudad extension of the intermediate mesoderm which previously gave rise to pronephric and mesonephric tubules This fact is sometimes overlooked in accounting for the anlage of the proximal as opposed to the distal portions of the nephron

*Development of Glomeruli*

There is no basic disagreement as to the development of the glomeruli It should be reemphasized, however, that the manner of origin of the glomeruli of the metanephric kidney is fundamentally the same as that for the pronephric and mesonephric glomeruli The very end of the tubule as it lies beneath the capsule is cupped by an advancing cluster of capillaries The inner layer of what was originally terminal tubular epithelium closely invests each of the capillaries and, together, these form the malpighian tuft Whether or not the capillaries carry into the tuft a stromal intercapillary mesangium which survives in the adult kidney, and participates significantly in pathologic processes, is a debatable matter to be discussed further under "Anatomy" and "Diabetes" In the developing kidney, the glomeruli are progressively larger as they approach the medulla (plate 7 A) No scars of the glomeruli, which are usually stated to disappear in the early stages of development, are noted The evidence is not satisfactory that resorption of the initial generations of glomeruli occurs

*Neonatal Growth*

The total number of glomeruli that the kid-, is destined to have is said to be present at birth or even prior to this time, when the fetus weighs between 2100 and 2500 Gm This impression seems not to be altogether correct insofar as there is evidence commonly of glomerular formation still going on in the kidneys of newborn full-term infants (plate 5 B). However, this process terminates shortly after birth.

It is estimated that about 1,300,000 nephrons are present in each kidney, although figures of various observers range from somewhat less than 1,000,000 to 4,500,000. The increase in size of the kidney that occurs with adult development results from enlargement of the various components of the nephron, particularly elongation of the tubules, rather than from an increase in the number of nephrons. It is remarkable that the glomeruli of adults have only a slightly greater diameter than those of infants, or even of the fully formed glomeruli of fetuses. However, the kidneys of larger species have considerably more nephrons than those of small species. For example, the relatively small size of the kidney of the adult rat in contrast to that of the human adult is due not merely to the larger cells and longer nephrons in the human, but to the greater number of nephrons There are approximately 34,000 nephrons in each kidney in the rat as against about 1,300,000 nephrons in the human kidney, the average diameters of the glomeruli are about 125 microns and 200 microns respectively

These data bear on the question of the morphologic nature of compensatory enlargement of a kidney following contralateral congenital hypoplasia or nephrectomy. The compensatory increase in size is a well known phenomenon in humans; in rats, it has been observed experimentally that after unilateral nephrectomy, the remaining kidney increases 70 per cent in weight in 40 days (Addis and Lew) This enlargement has been attributed by some to hypertrophy of the cells of the glomeruli and tubules, and by others to hyperplasia of their component cells The correct answer undoubtedly is that compensatory enlargement is the result of both hypertrophy and hyperplasia of cells (Rollason).

*Vestiges*

The embryologic development of the reproductive and urinary systems is so closely allied

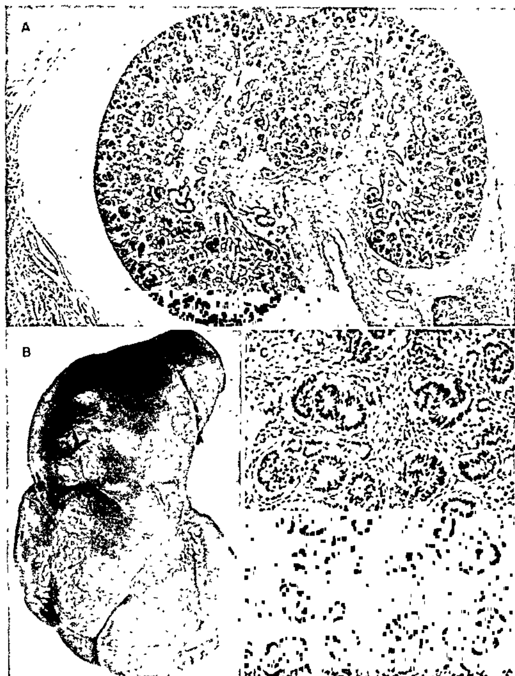



FIG A *Kidney from a 6 7 cm human fetus* illustrating a single interlobular fissure

FIG B *Residual fetal lobulations* of adult kidney which are commonly present

FIG C *High power of fissure* illustrated in figure A The glomeruli nearest the fissure are the most immature, corresponding to those beneath the capsule

that it is to be expected that vestiges of this linkage persist into postfetal life (plate 2 F) The gonads, both testes and ovaries, arise as ridges (germinal ridges) along the ventral border of the mesonephros The anatomic relationship is so intimate that the mesothelial covering of the developing gonad is immediately adjacent to and continuous with that of the mesonephros. The underlying mesenchyme then differentiates into the seminiferous tubules and stroma of the testis, or into ovarian follicles and stroma

*In the male*, the testis economically appropriates the mesonephric (wolffian) duct as the vas deferens, and the auxillary structures, namely the head of the epididymis, the seminal vesicles, and the ejaculatory ducts are formed from its distal portions The pronephric and most of the mesonephric tubules normally disappear by the end of fetal life Those mesonephric tubules which do not degenerate completely, comprise a cranial and a caudal group. The cranial mesonephric tubules are converted into the efferent ductules of the epididymis, except for a few which form the appendix of the epididymis The appendix of the testis represents the vestigial trace of the cephalic end of the mullerian duct The entire caudal group of the mesonephric tubules becomes vestigial as the paradidymis and the aberrant ductules

*In the female*, an entirely new duct originates beside each of the mesonephric ducts from a pinched off cylinder of celomic mesothelium This structure, known as the mullerian duct, subsequently differentiates into the fallopian tubes, uterus, and vagina. The mesonephric tubules and ducts in the female do not persist as important structures as they do in the male However, the proximity of the mullerian duct to the mesonephros leads to certain vestigial mesonephric traces associated with the reproductive system The cranial group of mesonephric tubules and a remnant of the mesonephric duct become the *epoophoron* and *paroophoron*, which correspond to the epididymis in the male. The more distal portion of the mesonephric duct (the vas deferens of the male) begins to atrophy at about the third fetal month in the female, and persists as Gartner's ducts These may be found at any level between the epoophoron and the hymen, especially along the broad ligament close to the uterus and vagina These vestigial structures may form cysts of a size sufficiently large to be clinically significant.

### *Position of Fetal Kidneys*

There is considerable change in the position of the kidney during its fetal development. Early in embryonic life, the kidneys lie in the pelvic cavity, immediately distal to the bifurcation of the aorta From this position, they move cephalad, clearing the arterial bifurcation so that by the ninth week, they lie against the dorsolateral body-walls, and are rotated a quarter turn so that their convexities are placed laterally rather than dorsally

## References


Addis, T, and Lew, W The restoration of lost organ tissue The rate and degree of restoration J Exper Med 7: 325–333, 1940

Arey, L B Developmental Anatomy A Textbook and Laboratory Manual of Embryology, 5th Ed Philadelphia, Saunders, 1946

Needham, J Biochemistry and Morphogenesis London, New York, Cambridge University Press, 1942 p 320

Patten, B M Human Embryology. Philadelphia, Blakiston, 1946

Potter, E L, and Thierstein, S T., Glomerular development in the kidney as an index of fetal maturity J Pediat 22: 695–706, 1943

Rollason, H D Compensatory hypertrophy of the kidney of the young rat with special emphasis on the role of hyperplasia Anat Rec 104: 263–285, 1949

# 2. Anatomy

## Gross Anatomy

The kidneys are situated retroperitoneally in the posterior part of the abdomen, on either side of the vertebral column and surrounded by layers of fat, fascia and areolar tissue The upper poles of the kidneys are approximately at the level of the 12th thoracic vertebra, their lower poles border at the 3rd lumbar vertebra The right kidney is slightly lower than the left, a circumstance usually ascribed to the limiting position of the liver The long axis of each kidney is directed downward and laterally, the transverse axis posteriorly and laterally

Each kidney measures about 11 x 6 x 2 5 cm, the left being somewhat longer and narrower then the right The kidneys of the adult male weigh from 125 to 170 Gm each, those of the female weigh 115 to 155 Gm each The weight of the kidneys tends to vary slightly with the habitus of the individual The combined weight of the kidneys is about 1/240 of the total body weight, in the newborn, the kidneys are relatively three times as large The weight of the kidney at different ages is about as shown in table 1 (Coppoletta and Wolbach)

### *Relations of the Kidneys*

The anatomic relations of the kidneys to adjacent viscera obviously differ on either side (plate 8) The left kidney is placed slightly higher than the right, presumably, so to speak, because of the hepatic barrier to the upward migration of the right kidney The upper poles of the kidneys lie at about the level of the 7th costal cartilage (eleventh rib posteriorly) and the 12th thoracic vertebra, with the right kidney about 1–2 cm lower than the left The lower poles of the kidney are at the level of the upper part of the 3rd lumbar vertebra

*Anteriorly*, on the right, an upper segment is covered by the adrenal gland, the lower segment by hepatic flexure, and the mesial or hilar area, by the descending part of the duodenum The largest remaining portion, laterally between the two poles, is covered by the liver The anterior surface of the left kidney is covered at its respective poles by adrenal gland and splenic flexure of the colon, mesially by stomach, pancreas and jejunum, and laterally by the spleen over an area almost as large as that overlain by the liver on the right The areas in relation to adrenal, duodenum, colon and pancreas are devoid of peritoneum, the areas contacted by liver, small intestine, spleen, and, as a rule, stomach are covered by peritoneum

Table 1 —*Weight of Kidney at Different Ages*

| Age | Grams | Age | Grams |
|---|---|---|---|
| Birth–3 days | 13 | 14 months | 36 |
| 3–7 days | 14 | 16 | 39 |
| 1–3 weeks | 15 | 18 | 40 |
| 3–5 | 16 | 20 | 43 |
| 5–7 | 19 | 22 | 44 |
| 7–9 | 19 | 24 | 47 |
| 2–3 months | 20 | 3 years | 48 |
| 4 | 22 | 4 | 58 |
| 5 | 25 | 5 | 65 |
| 6 | 26 | 6 | 68 |
| 7 | 30 | 7 | 69 |
| 8 | 31 | 8 | 74 |
| 9 | 31 | 9 | 82 |
| 10 | 32 | 10 | 92 |
| 11 | 34 | 11 | 94 |
| 12 | 36 | 12 | 95 |

The *posterior* surfaces of the kidney are in relation to muscles This surface is altogether devoid of peritoneum, is embedded in fat and areolar tissue, and lies on the diaphragm, the psoas major, the medial and lateral lumbocostal arches, quadratus lumborum, the tendon of the transversus abdominus, the subcostal and one or two upper lumbar arteries, and the last thoracic, iliohypogastric and ilioinguinal nerves In addition, the upper pole on the right rests on the twelfth rib, the left on the eleventh and twelfth The diaphragm separates the upper renal poles from the phrenicocostal sinus, although occasionally, the muscular fibers of the diaphragm are defective

in this region in which case the pleura is in direct contact with perirenal areolar tissue

The hilar structures include the nerves, renal vein, renal artery and ureter The latter three structures are placed in this order with the vein anteriorly, although frequently the ureter is located anterior to the vessels

### *Fixation of Kidney*

The kidneys are not as rigidly fixed to the posterior abdominal wall as is generally taught Moreover, inasmuch as they are in contact with the diaphragm, the kidneys—and to a corresponding degree, tumors of kidneys—may move slightly with the diaphragm during respiration Actual measurement of renal mobility with the aid of a fluoroscope revealed the range in normal adults to be from 0 1 cm to 6 5 cm (Moody and Van Nuys) The kidney and its hilar contents are surrounded by fibrofatty tissue called the *adipose capsule* which, in turn, is enclosed in the *renal fascia* It is clear that the position of the kidney is maintained largely by the attachments of the renal fascia and the cushioning of adjacent viscera Defects in such attachments—congenital or acquired—predispose to nephroptosis.

### *Renal Fascia*

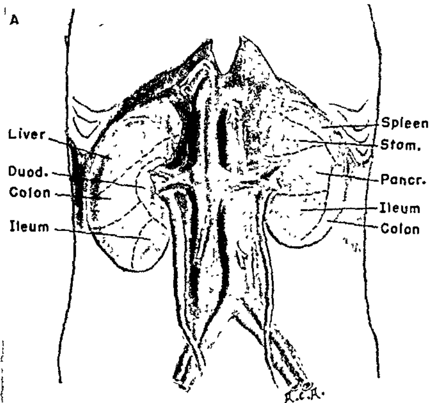
The details of the gross anatomy of the renal fascia are still the subject of some controversy It is generally agreed, however, that the renal fascia is a tough areolar membrane which is continuous with the subperitoneal fascia and splits into an anterior and posterior layer to invest the kidney (plate 8B) The fascia is separated from the true renal capsule by perinephric fat into which it sends fibrous trabeculae. The fat that lies behind and lateral to the renal fascia is termed the *paranephric body*. The two layers fuse superiorly with the fascia of the diaphragm The same layers enclose also the adrenal without the formation of a complete septum between the adrenal and kidney except in rare instances Medially, the layers blend with the areolar tissue about the great vessels at the root of the mesentery and behind the pancreas and duodenum (Mitchell) According to Grant and most observers the fascia does not blend medially with the adjacent connective tissue, but passes in front of and behind the renal vessels, the aorta, and the inferior vena cava to join the corresponding layers of the opposite side. These features are of importance in the migration of perinephric abscesses. The posterior fascia unites medially also with the fascia of the quadratus lumborum and the psoas major. Laterally, the anterior and posterior layers fuse directly. Inferiorly, it is generally stated that the two layers do not unite but merge separately with the fascia of the iliac fossa Mitchell, on the other hand, *finds that fusion of the layers does occur inferiorly*, but that the union is not as firm as it is superiorly, so that perinephric injections or accumulations of fluid (purulent exudate) may escape, particularly in the vicinity of the ureter

### *Nephroptosis*

The diagnosis of nephroptosis as well as ptosis of other viscera is now less commonly made than formerly when it was somewhat in fashion. Part of the reason for the reluctance to make the diagnosis is, first, the improvement in diagnostic methods, and, second, the realization that the kidneys normally are characterized by a degree of mobility or "floating," which is of the range of 0 1 to 6 5 cm (Moody and Van Nuys) Nevertheless, occasional cases with symptoms proved to be produced by abnormal renal mobility do occur. These symptoms include lumbar or abdominal pain, rarely simulating Dietl's crisis (intense pain, vomiting, collapse) because of angulation or torsion of the ureter Fatigue and gastrointestinal symptoms are mentioned prominently, albuminuria of the orthostatic variety may occasionally occur in nephroptosis, as may urinary stasis with infection

#### *Etiology of nephroptosis*

It is recognized that the kidney is maintained in its normal position by the vascular attachments of the pedicle, the adjacent



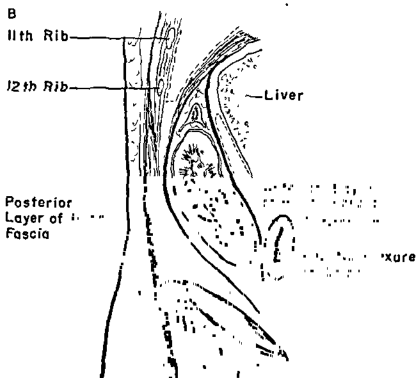




FIG. A *Relation of kidneys to viscera* (Anterior view) FIG B *Renal fascia* Sagittal view (After Gerota)

fascias, fat, and peritoneum, the support of neighboring organs, and the intra-abdominal pressure afforded by tonus of abdominal and back muscles Hence, anomalies, local trauma, body habitus, emaciation, improperly supporting corsets, pregnancy, retroperitoneal tumors or other masses (which, having displaced the kidney, at times to extreme positions (Greene), are subsequently removed), and cystocele with consequent elongation of the ureters, all predisposed to nephroptosis An observation recently made by Herbst is that in a number of cases of nephroptosis, unrelieved by nephropexy, the reason for the unsuccessful therapy was an abnormal, posteriorly located pelvis.

## Macroscopic Structure of the Kidneys

### *Capsular Surface*

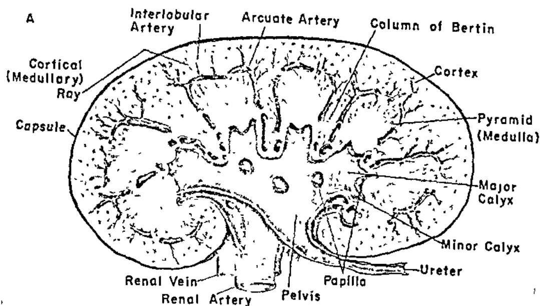
The kidney is enclosed by a thin, translucent fibrous capsule which may easily be stripped off A variable number of capsular blood vessels (veins and arteries), with caliber often as great as 2–3 mm , penetrate the capsule into the renal parenchyma so that when the capsule is removed, these vessels are torn The adipose capsule is cleanly separable from the renal capsule unless bound to it by adhesions from chronic perinephric inflammation (plates 25 A, B, and 167 A) Similarly, the renal capsule may be thickened and densely adherent to the capsular surface of the kidney as a result of parenchymal scarring following vascular disease and nephritis of various kinds The capsular surface of the kidney is normally light purple-red and smooth, except for the fairly frequent persistence of the fissures of the original fetal lobulations The stellate veins are usually clearly visible on the surface and tend to arrange themselves along the lines of the persistent or obliterated lobular markings (plate 50 A) Inflammations and degenerations pit and scar the surface and alter its normal coloration often in a pattern which, by itself, suggests the pathogenesis Petechial hemorrhages may indicate malignant nephrosclerosis (plate 211), acute diffuse glomerulonephritis (plate 54), focal endocarditic glomerulonephritis (plate 85 A), or a hemorrhagic diathesis Occasionally, casts of hemoglobin in the distal convoluted tubules simulate hemorrhages grossly (plate 167 A).

### *Hilum*

The *hilum* of the kidney expands into a *renal sinus* which is lined by a continuation of the capsule, and which contains the pelvis, calyces, vessels and nerves embedded in fat (plate 9). The amount of fat is variable, and is dependent on the degree of atrophy of the kidney and somewhat on general obesity (plate 278 C). The fatty overgrowth (lipomatosis) may be so extensive as practically to replace the kidney The renal pelvis—the funnel-shaped expansion leading into the ureter—is formed by the union of three major calyces, which in turn represent the junction of about twelve minor calyces (plate 11) The terminations of the minor calyces are cup-shaped, fitting snugly about one, or occasionally two or more, papillae, in a manner that permits efficient collection of the droplets of urine from the ostia of the papillae Spirally arranged muscles about the calyces are regarded as having a milking action on these tubes, thereby aiding the propulsion of the flow of urine (plate 11 B, C).

### *Sectioned Surface*

The sectioned midvertical surface of the kidney reveals a peripheral cortex and inner medulla (plate 9) The adult cortex averages 4–6 mm. in thickness, is reddish-brown and arches over the inverted bases of the pyramids except where it alternately dips between the pyramids as the *columns of Bertin*, which extend to the renal sinus The cortex is characteristically thickened in acute diffuse glomerulonephritis, chronic glomerulonephritis with edema ("lipoid nephrosis"), hemoglobinuric nephrosis and amyloidosis In the nephrotic syndrome of whatever cause, the cortex tends not only to be thickened, but to be colored yellowish because of the tubular lipid principally Wedge-shaped, pale, greyish-white cortical areas often represent foci of acute or subacute pyelonephritis An excessively edematous sectioned surface is frequently noted in acute glomerulonephritis, acute interstitial nephritis, hemoglobinuric nephrosis and cho-



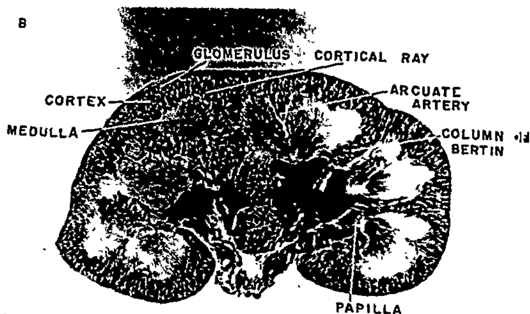




FIG A *Longitudinal section of the kidney* (Drawn after Brödel in Kelly and Burnam's *Diseases of the Kidneys, Ureters and Bladder*, New York, Appleton-Century, 1922 )

FIG B *Longitudinal section of the kidney*

lemic nephrosis, in the latter instance, the icteric staining of the kidney may be apparent

With careful examination, particularly under oblique light, the glomeruli may usually be seen as purple-red dots which appear slightly elevated from the surrounding surface (plate 10) Estimations of variations in size and color of the glomeruli as well as of the remainder of the sectioned surface, frequently afford some clue as to the nature of the pathologic processes For example, in most forms of acute diffuse glomerulonephritis, the ischemic glomeruli are enlarged and greyish-white, in sicklemia, the glomeruli are obviously congested (plate 270)

The medullary substance is made up of 8 to 18 *renal pyramids* (of Malpighi), each measuring about 1 5 cm in length and 0 5 cm across the base. The collecting tubules, for most of their length, are located in the pyramids, but extend into the cortex as striations or *medullary rays* (of Ferrein) The loops of Henle are also included in the medullary rays which represent longitudinal sections of these loops, the collecting tubules, and the peritubular capillaries Congestion of the radiating peritubular capillaries and the vasa recta is particularly conspicuous in hemoglobinuric nephrosis The apices of the pyramids are the renal papillae which project into the lumens of the minor calyces The base of the pyramids delineate cortex from medulla and, at this level, the arcuate artery is seen in cross section, or in longitudinal section arching over the base The pyramids can be subdivided into units called *renal lobules*, of which there are about 20,000 in each kidney

### *Renal Lobule*

The nomenclature of renal vessels implies the existence of renal lobes and lobules Actually, there is a difference of opinion as to what precisely constitutes a lobe or lobule By one definition, a lobule is made up of the wedge-shaped area extending from its apex in the papilla to the cortex It includes fused collecting tubules distally and fans out toward its base in the cortex to take in a medullary ray and surrounding renal corpuscles and convoluted tubules, with the interlobular artery at the periphery The other point of view places the interlobular artery in the core of a lobule so that the interlobular artery would be called intralobular by those who prefer this definition of a lobule

## Histologic Appearance

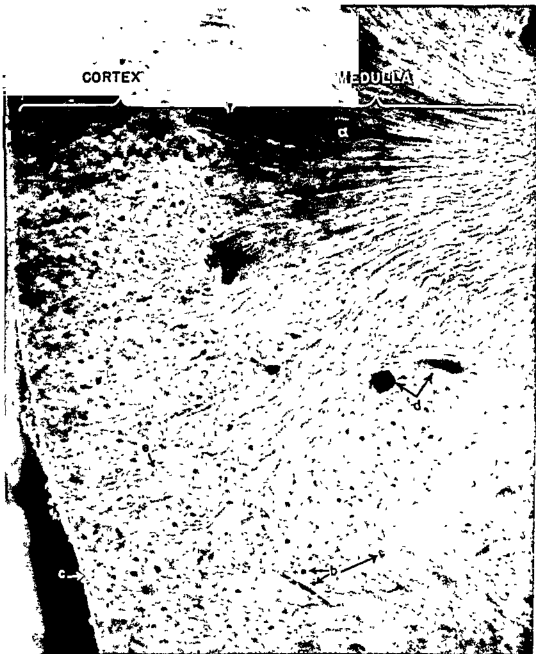
The nephron consists of the glomerulus, the so-called secretory portion of the tubular system extending through the distal convoluted tubules, and the excretory or collecting portion (plate 12 A)

### *Glomerulus*

The glomerulus, or renal corpuscle, averages 200 to 250 microns in diameter and approximately 0 0042 cu mm. in volume The total number of glomeruli has been variously estimated at from less than 1,000,000 to 4,500,000 (Verney) in each kidney, but the most generally accepted estimate is about 1,300,000 (Moritz and Hayman) The surface area of the loops of the glomerular capillaries in both kidneys is in the vicinity of 1.56 square meters. The glomerulus consists of Bowman's capsule and the malpighian tuft (plate 12 B) The capsule is composed of a parietal and visceral layer resulting from the invagination of the original epithelial vesicle, the primordium of Bowman's capsule, by a tuft of capillaries The parietal layer is lined by epithelial cells which are continuous, on the one hand, with the epithelium of the visceral layer, and on the other, with the epithelium of the neck of the proximal tubule The parietal epithelium is usually flattened so as to resemble endothelium, but occasionally it is elevated to the level of tall cuboidal cells Special significance has been attached to the increased height of the parietal epithelium, but this remains to be proved. Under various pathological conditions these epithelial cells become swollen with fat or eosinophilic granules, or may proliferate to form a crescentic cup over the tuft (plates 62, 63).

#### *Bowman's capsule*

The parietal epithelium rests on Bowman's capsule which normally is a thin membrane possessing an affinity for stains similar to that of collagen except for its argyrophilia (plates




*Section of the kidney* magnified 14 times, showing cortex and medulla Also indicated are (a) dark streaks of medullary peritubular capillaries, (b) glomeruli, (c) capsule, (d) arcuate arteries, and (e) cortical ("medullary") ray (A F I P Acc 37800)

21 A, C) The abnormal changes in the membrane consist in its becoming thickened by fibrinoid alteration, amyloid degeneration or collagen, and it may become fused with the malpighian tuft

*Malpighian tuft*

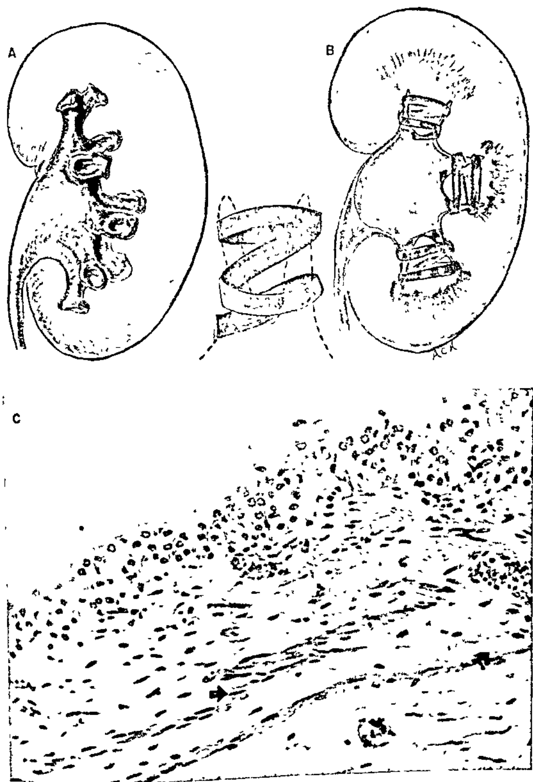
The vascular portion of the glomerulus constitutes the malpighian tuft At the vascular pole, or hilum of the glomerulus, the afferent arteriole invaginates the Bowman's capsule, divides into 8 to 12 convoluted capillaries, which unite again at the hilum to emerge as the efferent arteriole (plate 12 B) There is some question as to whether or not each capillary divides into a number of secondary and tertiary branches in contrast to the pattern of plate 12 B No anastomoses between the glomerular capillary loops are known to exist The afferent arteriole is invested with an adventitia which tapers off a short distance beyond the hilum leaving the glomerular capillaries away from the hilum stripped of this outer coat which is then reformed in the same gradual manner to envelop the efferent arteriole at its exit from the tuft The presence of this concentration of adventitial collagen about the arterioles at the hilum, tapering toward the opposite periphery of the tuft has given rise to the impression that an arboreal mesangium exists to which clusters of capillaries are attached In other words, it is believed by many that an intercapillary supporting tissue is present which not only supports the capillaries and binds them to each other, but also divides the capillaries into lobules Such a conception of the tuft may seem feasible in a two-dimensional section, but it is not consonant with the three-dimensional reconstruction. The more credible evidence suggests that the tuft comprises the capillary divisions of the afferent arterioles which join to form the efferent arteriole, and that those capillaries are not held together by a mesangium, or intercapillary ligaments, but are covered normally merely by the visceral epithelium of Bowman's capsule. The sum total of the intercapillary collagen appears confined to the hilum and seems to be limited even there to the residual continuation of the adventitia of the arterioles of the vascular pole This point of view is supported by the photographic evidence in plate 19 A

The capillary endothelium rests on a normally thin argyrophilic basement membrane (plates 21 A, C) This membrane is easily detected in routine sections, if they are properly thin and well stained, even with hematoxylin and eosin (plate 20 A). Despite assertions to the contrary, abnormalities in the basement membrane, such as reduplication, splitting, thickening and fibrinoid alteration, may be observed with this routine stain. This fact is demonstrated in many of the accompanying photomicrographs The point is emphasized not because the hematoxylin and eosin stain is superior to other stains for this purpose, but because there is a tendency to fail to look for fine changes in the glomerular capillaries in such routinely stained sections. The Mallory-Heidenhain stain, the Lee-McGregor, the Masson, and the silver stains are particularly adapted for the more vivid photogenic demonstration of changes in the basement membranes and for the investigation of certain qualitative reactions With a Mallory-Heidenhain stain, for example, the basement membrane normally stains blue Fibrinoid degenerations may be colored variously, from light orange to brilliant red, apparently depending on the degrees of degeneration The tissue is best fixed in Zenker's solution for the Mallory, McGregor and Masson stains The silver stains often reveal changes hidden with the Mallory or similar stains Alterations of collagen or reticulin that may look similar in the Mallory stain may show distinctly dissimilar pictures with the silver stains Amyloid change in '' e glomerulus, diabetic glomerulosclerosis, lipid alterations of the afferent arterioles, the glomerular lesions of disseminated lupus erythematosus are all

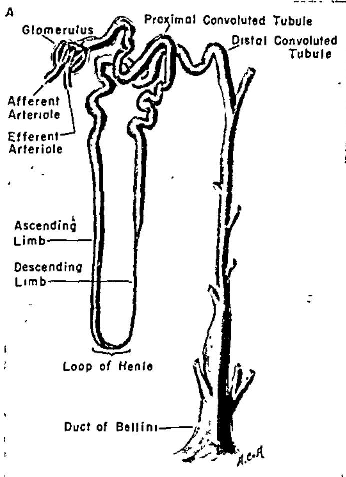
Fig A *Calyceal structure.* (Drawn after Brodel in Kelly and Burnam's *Diseases of the Kidneys, Ureters, and Bladder* New York, Appleton-Century, 1922 )

Fig B *Calyceal spiral muscle* which on contraction empties the calyx and strips the papilla as if by a milking effect (Drawn after Hinman, F., *Principles and Practice of Urology*, Philadelphia, W. B Saunders, 1935 )

Fig C Photomicrograph of calyceal spiral muscle (arrow)




(Legends on facing page)



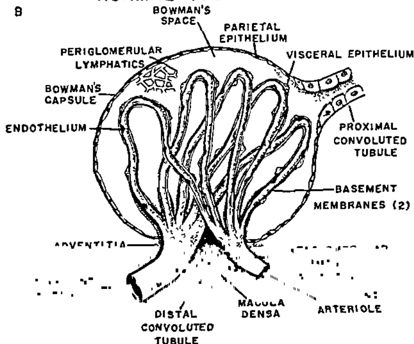
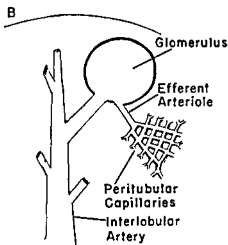




FIG. A The nephron

FIG B. The glomerulus.

A



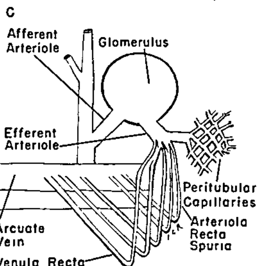
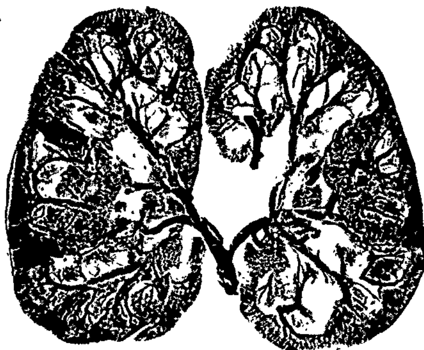
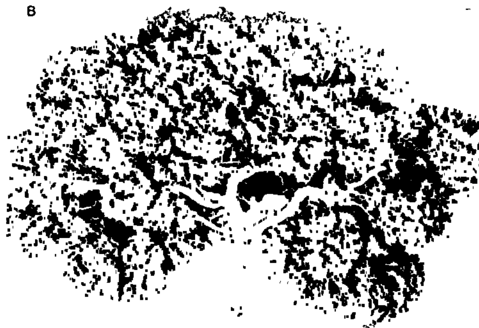




Fig A *Extra-glomerular shunts* via (1) a junction between the afferent and efferent arterioles, (2) Ludwig's arteriole from the afferent arteriole to the peritubular capillaries, (3) the arteriole from the interlobular artery to the peritubular capillaries, (4) vasa recta, (5) peritubular intercapillary anastomoses, (6) anastomoses with capsular vessels The arcuate vein (7), overlying the arcuate artery, receives the venulae rectae (8)

Fig B *Cortical glomerulus* showing wide afferent arteriole and short, narrow efferent arteriole in contrast to the juxtamedullary glomerulus

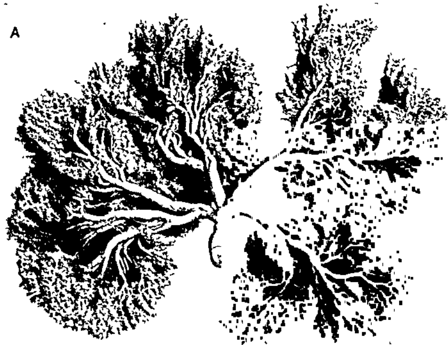
Fig C *Juxtamedullary glomerulus* characterized by the relatively more prominent efferent arteriole and the vasa recta into which it empties for the most part




... all as smaller branches are seen in this ... ugh ... ries

FIG B *The anterior surface of an entire neoprene cast* shows the divisions of the main renal arteries leading into a mop of the finest terminal ramifications which obscures the intermediate branches







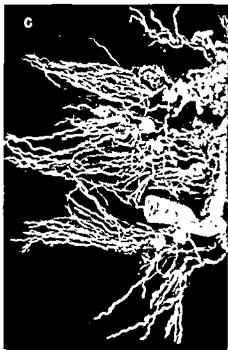



FIG A *A neoprene cast of the renal vasculature* separated to show the independence of the primary divisions and, in this instance, the more abundant supply to the anterior half

FIG B *A single interlobar artery* with branching arcuate, "subarcuate," and interlobular arteries along with many clusters of glomeruli

FIG C *Wide efferent arterioles* of juxtamedullary glomeruli form the straight parallel twigs of the medullary vasa recta (arteriolae rectae spuriae)







FIGS A AND B "*Subarcuate*" *artery* with many branches (interlobular arteries) leading to afferent arterioles, glomeruli and efferent arterioles, all of which can be discerned in these photographs.

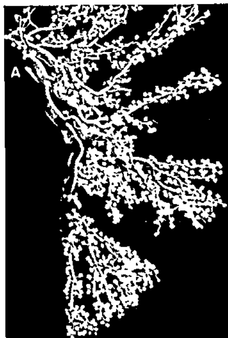












FIG. A *Interlobular artery, afferent arterioles and glomeruli*

FIG. C *Delicate afferent and long efferent arterioles* of glomeruli

FIG. B *The central tapering vessel* arises from an interlobular artery possibly to form an anastomosis with a capsular artery

FIG. D *Efferent arterioles* are seen to be of much thinner caliber than the afferent arterioles. The mesh reveals abundant intercapillary anastamoses

cases in point (plates 243, 244.). McGregor's and Masson's trichrome stains serve about the same purposes as the Mallory stains The special advantages claimed for the periodic acid-Schiff reagent technique, except for the demonstration of carbohydrates, are not apparent.

There are variable numbers of endothelial cells visible in a plane of section, but the *average is about 20 The remainder of the fixed* cells of the tuft are epithelial, average about 30, and unlike the spaced endothelial cells, lie as a syncytium closely applied to the outer surface of the capillaries

Presumably, the epithelial cells have a basement membrane of their own, analogous to Bowman's capsule (plates 12 B) This basement membrane has been described, but is most difficult to discern even with the very assiduously performed special stains The distinction between epithelial and endothelial cells is not always possible to make, but the relation to capillary lumen, when apparent, generally identifies the cells The evaluation of an increase of the fixed glomerular cells, as well as their enlargement and hyperchromatism is of importance in the diagnosis of certain types of glomerulonephritis Epithelial cells chiefly, but also endothelial cells, are phagocytic, as demonstrated for example, by their retention of malaria and melanin pigment, both cells may also contain fat (plate 76) Epithelial cells may undergo hyaline droplet or vacuolar degeneration (plate 112 D)

The *lumens* of the glomerular capillaries contain red blood cells with a scattering of white cells Ischemia of the capillaries, fibrinous thrombi, fused or agglutinated red blood cells, or extreme dilatation represent significant abnormalities

*Bowman's space* is normally about 7–14 microns wide Variations in width either through increase in size of the tuft, compression of the tuft by protein fluid in the space, or dilatation of the space as a result of increased pressure within the tubules, are changes to be evaluated Marked shrinkage of the tufts following formalin fixation may result in misleading prominence of Bowman's space Another variety of artefactual distortion of this space is produced by "protrusion" of proximal tubular epithelium into it In such "lesions," there is no evidence of stagnation of blood or other interference with glomerular circulation.

*Juxtaglomerular apparatus*

In the arch formed by the afferent and efferent arterioles is a group of closely packed cells to which, in recent years, important functions have been assigned by some investigators (Goormaghtigh, Kaufman), although the evidence is hardly complete. These cells forming the juxtaglomerular body (pohlkissen) appear to be continuous with the muscle cells of the afferent arteriole and efferent arteriole near the glomerular hilum; they have intermingled nerve fibers and are presumed to have the function of contractility, very much as myoepithelial cells (plate 12 B) The cytoplasm may be granular or fibrillar, and the variations in cytoplasmic phase have been regarded by some observers as indicative of an endocrine function The fibrils have been interpreted as myofibrils which regulate the caliber of the glomerular arterioles and thereby control intraglomerular pressure and filtration rate and fraction. Goormaghtigh suggests that these cells may act like the glomus cells which they somewhat resemble histologically, and shunt blood from the afferent arteriole to the efferent system, thus bypassing the glomerulus (Plate 20 C)

The juxtaglomerular body lies in contact with one wall of a distal convoluted tubule. The cells of this part of the wall, which are crowded together and have hyperchromatic nuclei, are known as the *macula densa*. The macula densa in combination with the juxtaglomerular body is referred to as the juxtaglomerular apparatus The function of the macula densa is even less understood than is that of the juxtaglomerular body although some observers have postulated a hormonal capacity on inadequate evidence (plate 12 B)

The size and number of cells in the juxtaglomerular apparatus vary considerably even in the one section of kidney. The determination of the normal range of such variation would require extensive and laborious micrometric surveys and statistical analyses, which appear not to have been done as yet. The best such study to date indicates that the average size of




FIG A *An afferent* arteriole supplying five glomeruli

FIG C *Long afferent arterioles* leading into glomeruli

FIG B *Glomeruli, afferent arterioles and interlobular artery*

FIG D *Glomerular structure* under high magnification The details of the malpighian tuft do not suggest the presence of an intercapillary mesangium

(These four plates of photomicrographs of neoprene casts were obtained through the generosity of Drs R H More and G Lyman Duff See Am J Path *27*:95-117, 1951 )

the apparatus is 40 x 70 microns with a range of 30–40 microns x 50–80 microns (Edwards). However, correlations of the size or number of cells of the juxtaglomerular apparatus with physiologic abnormalities, such as hypertension, are plainly hazardous, inasmuch as the measurements in these conditions fail to take the normal variations into sufficient account.

### *Blood Supply*

*Arterial*

The renal arteries come off the aorta at an oblique angle and enter the renal hilum where they divide into a dorsal and more extensive ventral set of branches (plates 14, 15) These are "end-arteries" without anastomoses. The first branches are the *interlobar arteries* which arise in the region of the pelvic fat and extend into the columns of Bertin between the medullary pyramids. The interlobar arteries lead into the *arcuate* (arciform) arteries which are grossly visible as they curve about the base of the pyramids These are the vessels which are likely to be involved in periarteritis nodosa and the evidence of this process may often be detected macroscopically. The next order of arteries arises perpendicularly from the arcuate arteries and extends radially into the cortex between the medullary rays. These vessels are known as either *interlobular* or intralobular arteries depending on the definition of the renal lobule, that is, on whether or not these vessels lie within the lobule or at its periphery. Recently, the term "*subarcuate*" has been applied to the more proximal portion of the interlobular arteries (More and Duff)

The interlobular arteries, often after branching (plates 16, 17), give rise to the *afferent arterioles* which extend into the glomeruli at their vascular poles or hilum. The afferent arteriole usually supplies a single glomerulus but may supply two or even several of them. In general, that is, in the outer cortical glomeruli, the afferent arteriole is longer than and about twice as wide as the efferent arteriole In the *juxtamedullary glomeruli* (about 15 per cent of all glomeruli) the caliber of the efferent arteriole is as great or greater than that of the afferent (Trueta et al.) (plate 13) In a given section it may be difficult to be certain of the identity of the two vessels unless by chance they are both in the same plane of section. Often the proximity of an arteriole to the interlobular artery indicates it is the afferent arteriole, inasmuch as the one arises from the other; in contrast, the efferent arteriole, after a short course, breaks up into peritubular capillaries or vasa recta, and therefore is not as likely to be in the immediate vicinity of the interlobular artery Moreover, the presence of elastic tissue and more conspicuous muscle fibers is additional presumptive evidence that

FIG A These 2 glomeruli, enlarged 35 times, are from a case of chronic sclerosing glomerulonephritis (Addis and Oliver) In none of these glomeruli is there a trace of a suggestion of the existence of intercapillary tissue (mesangium)

FIG B *Arteriolae rectae verae* arising principally from the arcuate artery to supply the medulla One arteriola recta spuria can be seen coming off an interlobular artery *There is no indication that the* arteriolae rectae verae are the efferent arterioles of obliterated glomeruli as some observers believe This kidney, including the vessels shown, was extensively infiltrated with amyloid

FIG C *Nephron from chronic sclerosing glomerulonephritis* The glomerulus is not included. The bulbous mass at the upper left is stated to have *eroded the adjacent, thin, vermiform segment* of the proximal tubule from a neighboring nephron The proximal tubule abruptly dilates into its terminal portion which continues as the loop of Henle into the distal convoluted tubules, and finally into a *collecting tubule*

The figures on the opposite page represent actual photomicrographs of portions of the nephron and vasculature of the human kidney, skillfully and meticulously teased apart, oriented and in-

(Courtesy of Dr Jean Oliver From *Architecture of the Kidney in Chronic Bright's Disease*. New York, Paul B Hoeber, 1939 )










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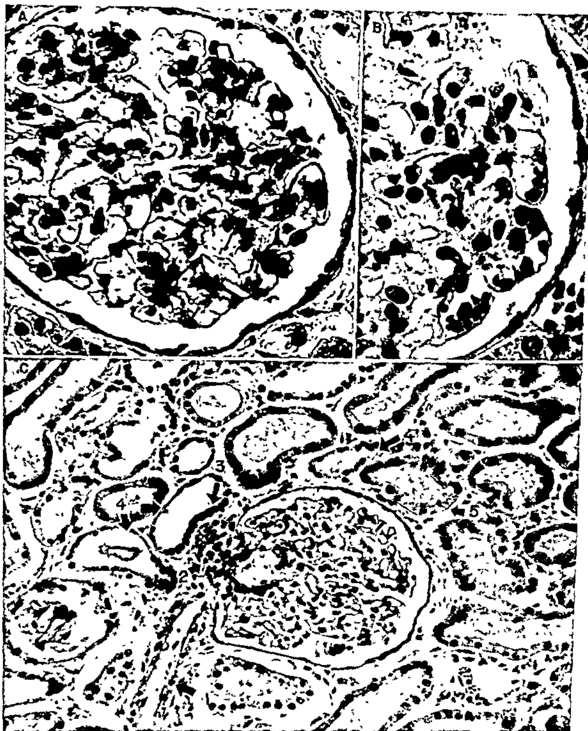



FIG A *Normal glomerulus* stained with hematoxylin and eosin showing capillary basement membranes, red blood cells, endothelial cells, epithelial cells, Bowman's space, Bowman's capsule and parietal epithelial cells

FIG B *Megakaryocyte* (arrow) within a glomerular capillary This is a fairly common normal finding which might be mistaken for metastatic cells of a neoplasm, particularly Hodgkin's disease

FIG C *Section of kidney showing glomerulus*, (1) afferent arteriole, (2) juxtaglomerular apparatus, (3) macula densa, (4) distal convoluted tubules, and (5) proximal convoluted tubules




Fig. A. *Normal glomerulus* showing argyrophilia of its capillaries and Bowman's capsule. (Bielschowsky's silver stain)

Fig. B. *Argyrophilia of elastica* of arcuate artery and vein, of tubular basement membranes and interstitial tissue. (Bielschowsky's silver stain)

Fig. C. *Wilder stain showing argyrophilia of basement membrane* of tubules, glomerular capsule and some glomerular capillaries of normal kidney. This particular method of staining does not adequately demonstrate the argyrophilia of *glomerular* capillaries or of their lesions.

the vessel is the afferent rather than the efferent arteriole Of course, serial sections allow unequivocal identification of the vessels

The medulla is supplied largely by *arteriolae rectae spuriae* or *vasa recta* which are parallel twigs formed by the efferent vessels of the juxtamedullary glomeruli Additional blood supply to the medulla is furnished by the *arteriolae verae rectae* which descend to the medulla as direct branches from the arcuate or interlobular arteries (plates 13, 15 C, 19 B) Some observers think that the arteriola vera recta is nothing more than the afferent-efferent arteriole merged as a result of glomerular degeneration. In any event, Trueta and his associates consider the vasa recta as the crucial intermediate pathway through which arterial blood is diverted from the cortex to the veins (*venulae rectae* of the medulla (plate 13) Evidence is being accumulated which provokes some doubt as to whether or not such a bypass actually functions, at least in dog and man (Kahn et al , Maxwell et al ).

*Veins*

The veins take origin from the capillaries of the outer cortex which, by confluence, form the *stellate veins*. The stellate veins which may be seen on the cortical surface (plate 25 B, 50 A) drain into the radially arranged *interlobular veins* and thence into *arcuate veins* after the pattern of the corresponding arteries. The arcuate veins receive also the blood from the straight *venulae rectae* which drain the medulla. The arcuate veins fuse to form the *interlobar veins* which give rise finally to the renal veins (Plate 13 A).

*Collateral circulation*

It is estimated that about 90 per cent of the blood normally flows through the glomeruli and that the remaining 10 per cent bypasses the glomeruli through the mechanism of shunts (plate 13 A) In other words, most of the blood in the peritubular capillary nets has less water, mineral salts and organic components than does the blood of the afferent arterioles, for example. There are five available pathways by which arterial blood may reach the renal parenchyma without traversing the glomeruli.

1. Arteriolar shunt from the afferent to the efferent arteriole.
2. Ludwig's arteriole from the afferent arteriole to the tubules, and a corresponding arteriole from the interlobular branch.
3. Anastomoses between peritubular capillaries.
4. Collateral circulation from vessels penetrating the renal capsule.
5. Arteriolae rectae from the interlobular and arcuate arteries to the medulla.

When the glomeruli or the immediately proximal portions of the afferent arterioles become obstructed, the shunts open. The extent of the extraglomerular blood supply utilized is dependent on the degree and rapidity of glomerular obstruction The obstruction may take the form of infarcts, small emboli, glomerulitis, vascular sclerosis, or angiospasm If the glomerular obstruction is rapid and severe, as in fulminating diffuse glomerulonephritis, the extraglomerular circulation may be inadequate to prevent necrosis of tubules. In more gradual processes, such as arteriolar nephrosclerosis, slow sclerosis of the glomerular capillaries with obliteration of their lumens leads usually to atrophy of the appertaining tubules, often with compensatory hypertrophy and hyperplasia of adjacent nephrons Possible exceptions exist in the glomerular nephrons of the human kidney which are believed to remain functional despite the obliteration of their glomeruli Apparently, in the instances of aglomerular nephrons, the burden of nourishment of the tubules has been adequately assumed by the extraglomerular blood supply It is of interest in this connection that in young goosefish, the glomeruli are connected with the tubules, but this linkage is lost in the adult and the kidney becomes functionally aglomerular (Grafflin).

The pathologic changes that are to be sought in the vessels are described under the individual diseases However, it deserves to be reemphasized that the presence of one or two histologically abnormal vessels—no matter how striking the vascular change may appear—does not necessarily prove that this abnormality was the cause of the associated renal failure. The interpretations of the arterial lesions of the typhus fevers, disseminated lupus erythematosus, and often of periarteritis nodosa bear on this obvious but frequently discounted principle.

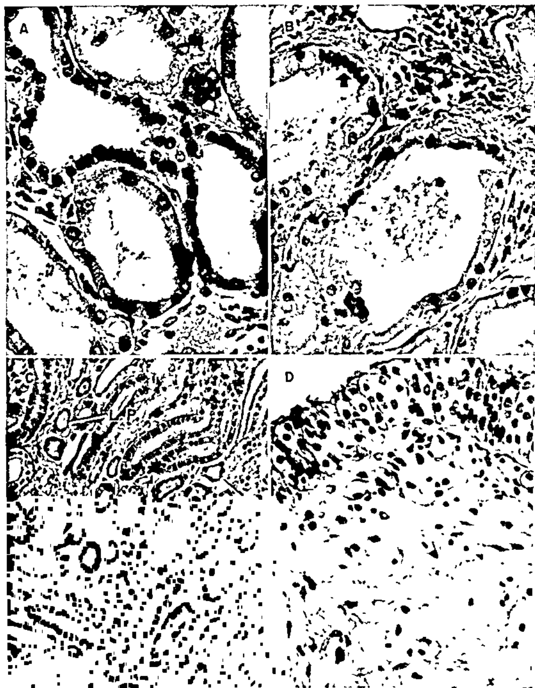



FIG A *Macula densa simulated* by closely packed nuclei of a distal convoluted tubule

FIG C *Normal medulla* showing cross sections of upper portion of descending limb of Henle, (D L ), lower portion of the descending limb (L P ), ascending limb (A L ) and collecting tubule (C T )

FIG B *Macula densa again simulated* by crowded cells which are obviously in proximal convoluted tubule (arrow) and hence could not be a true macula densa

FIG D Transitional epithelium of renal pelvis

*Tubules*

On the basis primarily of histological differences, the tubular portion of the nephron has been divided into several components (plate 12 A) In many basic respects, the structural differences are matched by differences in functional activity, as will be indicated in the chapter on physiology

*Tubular measurements*

*Proximal convoluted tubule*· approximately 60 microns in diameter and 14 mm. in length.

*Loop of Henle descending limb* approximately 14 to 22 microns in diameter and 4 to 10 mm. in length, *ascending limb* approximately 33 microns in diameter and 9 mm in length

*Distal convoluted tubule* approximately 20 to 50 microns in diameter and 4 6 to 5 2 mm. in length

*Collecting tubule* about 20 to 22 mm in length and 100 microns in width at the area cribrosa

*Total length of nephron* approximately 50 to 55 mm in length (Those nephrons beginning near the medulla (juxtamedullary) are longer than those with glomeruli at the outer periphery of the cortex )

*Total length of tubules in both kidneys* 120 kilometers (75 miles)

*Proximal tubules*

The proximal convoluted tubules average 14 mm. in length and 60 microns in diameter, and comprise not only the tortuous tubules of the proximal nephron, but the neck piece linking them to the glomerulus The proximal convoluted tubules constitute the bulk of the cortex and account for the fine granularity of the gross section These tubules are fairly easily identifiable by the characteristics of the lining cells, which are large, filled with small acidophilic granules, and lined on the luminal aspect by a brush border of cilia The basal portion of the cytoplasm is striated by perpendicular rods which stain like mitochondria In the superficial part of the cell, the mitochondria are granular Beneath the basement membrane of the brush border are a pair of centrioles and what is presumed to be a Golgi net demonstrable with suitable stains The position of the Golgi apparatus is said to change to the infranuclear position with compensatory hypertrophy. Enzymes—lipase, acid and alkaline phosphatase—are demonstrable in the epithelium of the proximal segment; the phosphatases are also present in the distal tubules, although an abundant amount of alkaline phosphatase is localized particularly to the brush border of the proximal convoluted tubules (Newman et al ). Additional enzymes, including oxidases, dehydrogenases, deaminases, carboxylases, glutaminases, esterases, hypertensinase and others are present in the kidney.

The cells of the entire length of the proximal convoluted tubules have a similar structure, but it is apparent from the selective effects of poisons (mercuric chloride, uranium nitrate) on the tubules, and from the varying gradients of absorption of glucose and vital dyes (Oliver, 1949) that there are three or perhaps four segments that are at least functionally different.

In approximately 15 per cent of individuals over 40—and rarely in younger people—there are found isolated clusters of about five or six epithelial cells in the proximal tubules (Harman and Hogan) (plate 23 D). The cells comprising these syncytia appear as if they have become fused or agglutinated so as to resemble a foreign body giant or the epithelial reaction to the proteid casts of myeloma, crystals of sulfonamides or calcium encrustations as noted in the distal tubules These collections of cells are similar also to the macula densa of the distal tubules The nuclei of these proximal syncytial masses are pyknotic, in contrast to the normal nuclei, but mitoses are not observed among them They are sufficiently common to suggest that they are an indication of a degenerative change of aging with no detectable functional significance.

Of all the cells in the kidney, those of the proximal convoluted tubule are particularly vulnerable to degenerative changes For example, in an area of early infarction, these cells may show coagulation necrosis, whereas those of adjacent distal convoluted tubules within the infarct may be preserved (plate 258 A) Similarly, the cells of the proximal convoluted tubules undergo postmortem degeneration earlier than the cells of the remainder of

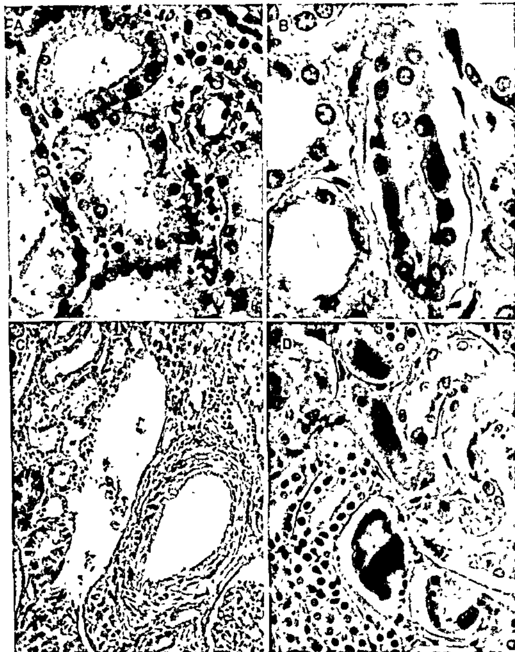



FIG A *Mitotic figure* in epithelial cell of proximal convoluted tubule

FIG C *Normal arcuate artery and vein* showing the intimate relation of the latter to tubules

FIG B *Mitotic figure* in epithelial cell of distal convoluted tubule

FIG D *Syncytial cell masses* of epithelium of proximal convoluted tubules occurring generally after the fourth decade

the nephron (plate 337 A). On this account, care must be taken not to mistake this artefact for tubular necrosis

*Loops of Henle*

The proximal tubule continues for variable short distances (about four-fifths of the limb in the outer cortical nephrons and about one-half of the limb in the juxtamedullary nephrons) as the upper portion of the descending limb of the loop of Henle and abruptly narrows into its thin portion. The descending limb measures 11 to 22 microns in diameter and loops into the thicker ascending limb (30 to 35 microns) The transition often occurs before the turn of the loop The length of the limbs, as indicated, varies with the position of the glomerulus, but averages about 5 mm. for the descending limb and about 9 mm for the ascending limb Those glomeruli near the capsular surface of the *cortex* have the shortest limbs and in some of these, the proximal tubules may lead directly into the ascending limb The deeper, or juxtamedullary glomeruli are attached to nephrons with long limbs measuring as much as 10 mm. or even more and extend to the apex of the papilla.

The cells of the proximal convoluted tubule change their character abruptly in the descending limb The brush border disappears, the cells become more flattened, the cytoplasm paler and more finely and homogeneously granular. The nuclei are about the same size and vesicularity as those of the proximal convoluted tubules, but tend to be more oval, as if compressed and occupy a greater volume of the cell than do the nuclei of the proximal tubules. The free edges of the cells have terminal bars and in the supranuclear position there is a pair of centrioles with a central flagellum not visible with ordinary stains Mitochondria are rare A Golgi net is said to be present The cells of the ascending portion of the limb are tall, cuboidal or short columnar, with rathe distinct cell boundaries. The base of the is faintly striated and appears more com and darker than the inner, luminal porti The nucleus is round or oval and in midposi in the cell.

*Distal convoluted tubules*

The distal convoluted tubule measures proximately 4.6 to 5.2 mm. in length and to 50 microns in diameter. Its cells have double centrioles but do not have the cilia border A suggestion of basilar striations be detected The cytoplasm is much less dophilic than the cytoplasm of the cells of proximal tubules There are about five to ei nuclei visible in a cross section of the di as against the three or four of the proxi tubules In the segment containing the mac densa there may be more than 20 nuclei i cross section The reason for the greater nu ber of nuclei in the distal tubule is the re tively larger amount of cytoplasm in the ce of the proximal tubule.

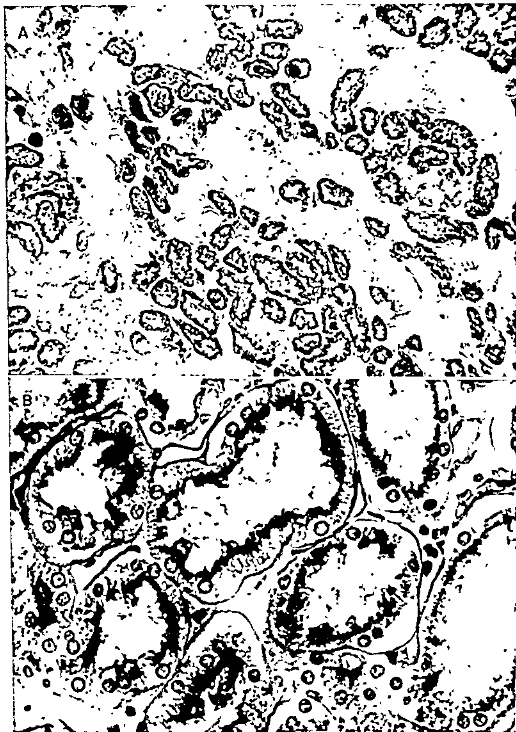
*Collecting tubules*

The system of collecting tubules begins the cortex with the so-called "periphe branchings" which unite the distal secreto tubules with the excretory tubules or the *me ullary rays* within the cortex. The medulla rays converge into the inner zone of the m dulla where they join at acute angles with simil tubules The junctions of progressively wid tubules occur at about seven levels until the end in large straight collecting tubules The are the *papillary ducts of Bellini* which ope into the minor calyces through the ostia of th *area cribrosa* of the apex of the papillae

The epithelium of the collecting tubules di fers from that of the secretory tubules. In th first part of the collecting system, the epithe lium is cuboidal with sharp borders, dark stain

FIG A *Alkaline phosphatase distribution* in the normal kidney is concentrated in the epithelium of the proximal convoluted tubules A trace is shown in the glomeruli (Gomori stain) Actually, various alkaline phosphatases, as well as acid phosphatases, are present not only in the proximal tubules, but also in the glomeruli, distal tubules, vascular endothelium and nuclei in other locations

FIG B *Alkaline phosphatase is localized* particularly to the cilia and luminal portions of the epithelial cells of the proximal convoluted tubules (Gomori stain) The phosphatase is presumed to play a role in the tubular reabsorption of glucose, as in the intestinal tract The principle of staining is similar to that for lipase and esterase




(Legends on facing page.)

ing nuclei and clear cytoplasm However, as in the secretory tubules, the epithelium contains a pair of centrioles and flagellum. The cells become progressively taller through the rest of the collecting tubules, but the other cytoplasmic characteristics remain about the same. The papillae are covered with transitional epithelium similar to that of the calyces (plate 22D). The length of the collecting tubules is about 20 to 22 mm

The *pathologic changes* that may occur in the tubules include the following:

1 hyaline droplet, hydropic and fatty alteration,
2. epithelial necrosis, regeneration and atrophy,
3. calcification of epithelium,
4. pigmentation of epithelium by hemosiderin, melanin, or lipochromes,
5. the inclusion of viruses, or simulating material, as well as bacteria, treponemas and fungi,
6. the dilatation of lumens,
7. the presence of various crystals,
8. disruption of tubular walls,
9 the accumulation of exudate and casts,
10 alteration of basement membrane by argyria, amyloidosis or collagenization,
11. neoplasia

### *Aglomerular Nephrons*

On the basis of his studies of the microdissected kidneys, Oliver has concluded that the tubules in human kidneys may function as nephrons without their appertaining glomeruli Bell sharply disputes this conclusion chiefly on the basis of his own investigations of the kidneys, not by microdissection, but with the aid of serial sections and a great experience with a wide range of renal pathology As far as Bell is concerned, atrophic glomeruli are associated with atrophic nephrons down to the collecting tubules He states that there is no evidence that the small atrophic segments of tubules which persist after obliteration of the glomeruli are really functional In the absence of more convincing proof of the *practical functional contribution* of aglomerular nephrons *in the human,* one cannot altogether dismiss the justification for Bell's skepticism On the other hand, advocates of the existence of these [a]glomerular nephrons in the kidneys of hu[mans] derive some phylogenetic comfort from [the] fact that in the toadfish, the sea horse, an[d] pipefish, essentially aglomerular kidney[s] abundant work and excrete most of the [uri]nary constituents of mammalian urine.

If aglomerular nephrons do exist—and [the] morphologic evidence of Oliver and his [asso]ciates suggests that they do—it is not l[ikely] that they are totally without function. Ph[ysio]logic evidence of this function is thus far l[ack]ing However, it is reasonable to believe [that] the tubules of such nephrons may excrete [sub]stances brought to them by the peritub[ular] capillaries Perhaps, with deprivation of t[heir] glomeruli, these tubules acquire an excre[tory] *capacity that they did not previously pos[sess].* It is of interest, in this regard, that the nor[mally] aglomerular kidneys of the animals mentio[ned] above are unable to excrete glucose, even w[hen] *the blood level of this substance is raised c[on]*siderably. In any event, practically speaki[ng] it is doubtful if the aglomerular nephrons of [the] human kidneys are of such common occurre[nce] as to represent a significant contribution [to] total renal function After all, when glomer[uli] become scarred, their appertaining nephr[ons] do generally disappear or become uselessly at[ro]phic. *Although the persistent aglomerular nep*hron, at most, is the exceptional nephron in [the] kidney of humans, it would nevertheless [be] fundamentally informative to try to pur[sue] Oliver's meticulous work to completion a[nd] to learn the functional properties of this ty[pe] of nephron in humans

### *Interstitium*

In the normal kidney, the interstitial tiss[ue] is hardly noticeable, particularly in the corte[x]. It is of the reticular type and includes a fe[w] scattered macrophages. At the apex of t[he] pyramids, and especially about the ducts [of] Bellini, the connective tissue is increased [in] amount and tends to take on an acidophil[ic] homogeneous character

Pathologically, the changes include edem[a], cellular infiltration, lipid and crystalline d[e]posits, amyloidosis, and neoplasia. The di[s]position, degree, quality and location of th[e]













FIG A *Residual normal capsule* after stripping of the outer capsule

FIG C *Normal capsule*, unstripped.

FIG. B *Stellate vein* anastomosing with capsular vein.

FIG D *Capsular artery* communicating with renal parenchyma.

edema and infiltrate varies with different diseases.

### *Lymphatics*

The lymphatic vessels are not readily seen in routine sections, but may be demonstrable by injections of dye or by the presence of metastatic deposits of cancer within the lymphatics (Rawson) Lymphatic networks are present in the capsule as well as in the renal interstitium and about the tubules Lymphatic vessels do not seem to penetrate the glomerular tuft but rather appear to surround the Bowman's capsule very much as a net about a sphere Usually, the lymphatic vessels about Bowman's capsule are collapsed and invisible in routine sections, unless dilated with metastases or with purulent exudate, as in some cases of acute exudative glomerulonephritis The parenchymal lymphatic vessels communicate with the perirenal lymphatics The larger lymphatic vessels leave the renal hilum beside the main blood vessels Valves are found in these large lymphatic vessels but are lacking in those of the parenchyma (Peirce) (plate 51A)

### *Renal Nerves*

The nerve supply of the kidney, especially the distribution of its finer ramifications, has not been worked out completely. However, it is known that the kidneys are richly supplied with autonomic nerves extending from the 4th dorsal segment to the 4th lumbar segment, with fibers also from the vagus nerve The autonomic (sympathetic) nerves reach the kidney with the greater, lesser and least splanchnic nerves Fibers from the greater and lesser splanchnic nerves synapse in the abdominal and splanchnic ganglia and then make up the renal plexus about the hilum of the kidney; the fibers from the least splanchnic nerve reach the renal hilar ganglion from which the postganglionic fibers enter the renal parenchyma From this plexus, nonmedullated fibers extend into the parenchyma along the afferent and efferent arterioles, between the cells of the renal tubules, and on the glomerular capsule.

The nerve endings are said to be distinctive and to resemble those of salivary glands (von Smirnow). Afferent fibers also exist in the renal pelvis which, when stimulated, give rise to pain and are said to be able to cause anuria by vasomotor control. The function of the vagal (parasympathetic) fibers is not definitely known. It is clear from explantation experiments in which the kidney is removed to the cervical region, for example, and the renal artery and vein are anastomosed to the carotid artery and jugular vein, respectively, that it may function without neural connections. Indeed, in such explanted kidneys, no consistent change in either blood flow or urea clearance was noted (Rhoads et al ). This fact does not diminish the importance of the direct and indirect neural influences on the glomeruli and vessels of the intact kidneys, such as appear to occur in shock and other forms of stress From a practical point of view, it is important to know that the related distribution of the autonomic nerves of the kidney and ureter and those of the gastrointestinal tract (splanchnic nerves, celiac and aortic ganglia) may cause lesions of the urinary tract to produce symptoms of disorders of the alimentary or biliary tract. The presenting, and sometimes the only symptoms in about 25 per cent of cases of disease of the kidney and upper ureters are nausea, vomiting, pain in the upper quadrant, constipation or diarrhea

### References


Addis, T., and Lew, W The restoration of lost organ tissue The rate and degree of restoration J Exper Med 7: 325–333, 1940

Bell, E T Renal Diseases Philadelphia, Lea and Febiger, 1946

Coppoletta, J M, and Wolbach, S B.· Body length and organ weights of infants and children Am J. Path 9: 55–70, 1933

Edwards, J G.: The vascular pole of the glomerulus in the kidney of vertebrates Anat Rec. 76: 381–389, 1940

Fahr, Th. Handbuch der speziellen pathologischen Anatomie und Histologie, Henke, F and Lubarsch, O, Vol 6 Berlin, J Springer, 1925

Gomori, G Distribution of acid phosphatase in tissues under normal and under pathologic conditions Arch Path. 32: 189–199, 1941.

Goormaghtigh, N.: Les segments neuromyo-arteri-

els juxta-glomerulaires du rein Arch. Biol, Paris, 43: 575-591, 1932
——: The renal arteriolar changes in the anuric crush syndrome Am J Path 23: 513-529, 1947.
GRAFFLIN, A. L. Pseudoglomeruli of the kidney of Lophius piscatorius Am J Anat 44: 441-454, 1929
GREENE, L F.. Extreme renal displacement due to retroperitoneal tumors J. Urol. 59: 174-178, 1948
HARMON, J. W, AND HOGAN, J M, JR Multinucleated epithelial cells in the tubules of the human kidney Arch Path 42: 29-36, 1949
HERBST, W P The posteriorly located renal pelvis associated with ptosis J A M A 137: 775-777, 1948
KAHN, J. R, SKEGGS, L T, AND SHUMWAY, N P. Studies of renal circulation Circulation 1: 445-453, 1950
KAUFMAN, W The Goormaghtigh cells in the normal and diseased human kidney Their possible relationship to human hypertension Am J Path 18. 783-797, 1942
McCANN, W S, AND ROMANSKY, M J Orthostatic hypertension The effect of nephroptosis on the renal blood flow J A M A 115: 573-578, 1940
McGREGOR, L The finer histology of the normal glomerulus Am J Path 5: 545-558, 1929.
MAXWELL, M H, BREED, E S, AND SMITH, H W Significance of the renal juxtamedullary circulation Am J Med 9: 216-228, 1950
MITCHELL, G A G The renal fascia Brit J Surg 37: 257-266, 1950
MOODY, R O, AND VAN NUYS, R G The position and mobility of the kidneys in healthy young men and women Anat Rec 76 111-133, 1940
MORE, R H, AND DUFF, G L The renal arterial vasculature in man Am J Path 27 · 95-117, 1951
MORITZ, A R, AND HAYMAN, J M, JR Disappearance of glomeruli in chronic kidney disease. Am J. Path 10: 505-518, 1934
OLIVER, J. Architecture of the Kidney in Chronic Bright's Disease. New York, Paul B Hoeber, 1939
—— The structure of the metabolic process in the nephron J Mt Sinai Hosp. 15: 175-222, 1948-49
PEIRCE, E C. Renal lymphatics Anat Rec 90. 315-329, 1944
RAWSON, A J. Distribution of the lymphatics of the human kidney as shown in a case of carcinomatous permeation Arch Path 47: 283-292, 1949
RHOADS, C P, VAN SLYKE, D O, HILLER, A., AND ALVING, A S Effects of novocainization and total section of nerves of renal pedicle on renal blood flow and function Am J Physiol 110. 392-398, 1934
ROLLASON, H DUNCAN Compensatory hypertrophy of the kidney of the young rat with special emphasis on the role of hyperplasia Anat Rec 104· 263-285, 1949
VON SMIRNOW, A E.. Über die Nervenendungen in den Nieren der Säugetiere Anat Anz 19: 347-359, 1901
TRUETA, J, BARCLAY, A E, DANIEL, P M, FRANKLIN, K L, AND PRICHARD, M M L Studies of the Renal Circulation Springfield, Ill, C C Thomas, 1947
VERNEY, E B Polyuria III Polyuria in chronic nephritis Lancet 1: 751-756, 1929
VIMTRUP, B On number, shape, structure and surface area of the glomeruli in kidneys of man and mammals Am J Anat 41: 123-151, 1928
VON MÖLLENDORFF, W Handbuch der mikroskopischen Anatomie des Menschen Vol 7, Pt 1 Berlin, J Springer, 1930
ZIMMERMANN, K W Über den Bau des Glomerulus der menschlichen Niere Ztschr f mikr-anat Forsch 18: 520-522, 1929

# 3. Normal and Abnormal Physiology

## Introduction

The zigzag development of our ideas on the physiology of the kidney parallels the detoured mode of advance in most fields of theoretic activity An epochal gain was initiated by Malpighi's announcement in 1666 that the medullary striae were not really fibers, but were tubes and that they were in continuity with globular "glandular" structures or glomeruli This conclusion was definitely proved by Bowman in 1842 with the help of the then popular method of injection of red lead. Bowman assumed that the urinary wastes reached the tubular lumens by the method of excretion through the epithelium, and that the role of the glomeruli was essentially to supply the water with which to flush these products down the nephrons Heidenhain subsequently modified Bowman's idea slightly by maintaining that not only did the tubules secrete the urinary constituents, but that salts as well as water entered the tubular lumen through the glomerular membrane

This concept was for a generation favored over Ludwig's theory that urine consisted entirely of the glomerular filtrate which had been concentrated by the tubular reabsorption of water through the process of simple diffusion Ludwig's explanation did not account for variability in degrees of concentration of the urinary solids which ought to have been equal with unselective diffusion For example, urea is concentrated about 60 times, whereas chloride is concentrated only twice During the early part of the twentieth century, convincing evidence was brought together to form the Cushny theory of filtration-reabsorption, according to which urine was composed of the glomerular filtrate minus what was *selectively* reabsorbed across the tubular epithelium into the peritubular capillaries Because the range of concentration of the solids of the glomerular filtrate was incompatible with simple diffusion on the basis of the known principles of osmotic pressure, it was hypothesized that some form of "vital activity" propelled the return of essential metabolities across the tubules in spite of an adverse oncotic gradient. This hypothesis still stands.

It must be admitted that little of comparably fundamental importance has since been added to our information on renal physiology. We have learned, for example, that enzymes occur within the kidney, enzymes that are concerned with the transtubular migration of glucose and enzymes that possibly are concerned with hypertension We have learned that the tubules may also excrete substances as an ancillary function and that the function may be measured, at least in the structurally normal kidney, by the clearance studies. We do not yet know why so tangible a process as pericarditis occurs in uremia, nor, except for the effects of hyperkaliemia, precisely what is the form of toxicity in uremia We are really just beginning to understand the vagaries of renal circulation, including, indeed, the finer anatomy, as well as the influence of shock, vasoconstriction, nervous stimulation, various hormones and therapeutic drugs Even the mechanism of anuria following the action of nephrotoxic agents is still highly controverted.

Obversely, for the many who continue to believe that morphology long ago yielded all the important information inherent in that subject, the awareness of the gaping hiatuses that exist in clinicopathologic correlation ought to dispel such an unproductive point of view. It would be pointless to pretend that we have been clear about the physiologic pathology of the many forms of tubular vacuolization, granularity, necrosis, proteid and pigment casts, juxtaglomerular apparatus, glomerular changes, and the nature of the various vascular alterations, to cite a few instances Even the mere identification of the many crystals that are noted in histologic sections of kidneys has not been refined over the past half century Exact knowledge of the composition of the crystals would undoubtedly furnish fruitful clues not

only about the pathogenesis of some of the renal diseases (as in cholemic nephrosis), but also information about the metabolic chain, particularly the end product, of certain materials, as is illustrated, for example, by the deposits of calcium oxalate crystals in ethylene glycol poisonings

In the ensuing chapters, considerations of the various aspects of renal diseases will be coupled, when feasible, with discussions of the pertinent altered physiology This current chapter is meant to serve as a basis for orientation on the general subject of renal physiology. Although much obviously remains to be worked out, and although some phases of dynamic renal physiology must be considered to have advanced a step from the dogmatic to the controversial level, there nevertheless remains a fairly solid conceptual framework on which to build

## Glomerular Function

The kidney contributes to the stabilizing homeostatic regulation of the internal environment by three processes

1 Removal by filtration of a portion of the blood plasma and its solutes (e g , potassium, sodium, chloride, sulfate, urea, glucose, amino acids, etc )
2 Selective tubular reabsorption
3 Tubular synthesis and excretion

The intimate and constant control of the constituents of the blood is facilitated by the fact that, at rest, 25 per cent of the cardiac output (1200 cc per minute, or 1700 liters per day) is apportioned to the kidneys, even though they comprise only a small fraction (0 5 per cent) of the body weight Such a disproportionate fraction of the cardiac output is made mechanically possibly, in the main, by the enormous capacity of the glomerular capillaries Of the 1700 liters or so that traverse the lumens of the glomerular capillaries during the course of a day, 170 liters, or 10 per cent, of the volume is removed from the blood in the form of glomerular filtrate. From this abundant filtrate, only about one liter of urine is formed and the remainder of the filtrate is returned to the blood by reabsorption across the tubular epithelium into the peritubular capillaries and vasa recta. The glomerular capillaries are distinctive in (1) their location between two arterioles, afferent and efferent, (2) the level of the blood pressure (75 mm Hg) which is approximately twice that of other capillaries, (3) their double wall including both an endothelial and epithelial basement membrane as well as epithelial cells located external to the membranes, and (4) their concern with filtration alone rather than with filtration and reabsorption as in the case of other capillaries

### *Filtration*

Glomerular filtration is the resultant of several hemodynamic forces and the organic integrity of the glomerular capillaries The hemodynamic forces are: (1) hydrostatic pressure of the capillaries which normally averages 75 mm Hg, and (2) the osmotic pressure of about 25 mm Hg, exerted by the constituents of the plasma which is augmented by an intracapsular tissue pressure (or the pressure in Bowman's space) of about 10 mm Hg The effective filtration pressure is, therefore, normally 75 − (25 + 10) or 40 mm of Hg An increase in the capillary pressure causes an increase in filtration pressure and hence in the filtration rate With decrease in glomerular capillary pressure to less than 40 mm Hg, as may occur in shock, the filtration pressure may be lowered to a degree sufficient to cause anuria Variation of either of the two other vectors produces obvious, corresponding alterations in the filtration For example, if the capillary pressure remains constant, an elevation of intrarenal pressure or of intracapillary oncotic pressure works in the direction of decreasing filtration pressure and filtration rate A decrease in osmotic pressure by itself, such as may occur in hypoproteinemia, increases filtration pressure and rate If all three factors are constant, that is, the capillary, the osmotic and the tissue pressures, then an increase or a decrease in blood flow results in a corresponding change in filtration rate

### *Regulation of Glomerular Function*

The advances in recent years in the field of renal function have been centered on the critical mechanisms of regulation of renal cir-

culation Previously, it was apparent that the renal vessels possessed great lability in their response to chemicals or the stimulation of nerves For example, it was known that adrenalin produces vasoconstriction, and that urea, glucose, sodium bicarbonate and xanthines cause vasodilatation, that reflex stimulation of the vasoconstrictor center narrows renal vessels, and that repeated stimuli to the 11th and 12th dorsal fibers provoke vasodilatation And so, the renal response to excitement, hemorrhage, cardiac decompensation, and other homeostatic alterations was presumed to depend on this gross basis However, it is now clear that the adjustments in the circulation hinge on the most sensitive response by fine, nicely balanced, strategically placed structures. Among such structures, the efferent arterioles loom especially important

In the first place, it is a fact that the formation of urine increases with constriction of efferent arterioles and elevated renal blood pressure, and decreases in reverse circumstances. However, along with vasoconstriction (produced by adrenalin or stimulation of the reflex vasoconstrictor center of the rabbit) the volume of the kidney expands The injection of adrenalin may be demonstrated, by direct observation and measurement in the frog, to increase the size of the glomeruli and to elevate the pressure in their capillaries (Richards and Schmidt) This expansion is attributed to distention of the glomerular capillaries as a result of constriction of the efferent arterioles, with consequent narrowing of the glomerular vascular outlet and raising of the intraglomerular vascular tension It is on the intraglomerular pressure that the important function of renal filtration (and possibly even systemic blood pressure, in at least some instances) has close bearing The efferent arterioles, then, constitute the order of renal vascular ramifications that is of key significance.

It remains to be shown whether or not vaso-

. . .

due actually to the normally smaller caliber of the efferent arteriole on which slight vasoconstricting action would exert relatively greater effect than it would on the afferent vessel.

There is another differential consideration involved in the glomerular circulation. The blood in the efferent arteriole differs from that in the afferent vessel by virtue of the loss of water and other urinary constituents and the consequent increased viscosity. The possibility that some of the urinary constituents may have a vasodilating action on the afferent side of the glomerulus, prior to their filtration, is to be considered.

*Neural Control of Glomerular Blood Flow*

From the time of Claude Bernard's contributions, it has been known that the splanchnic nerves can experimentally be shown to influence dramatically the flow of urine In dogs and rabbits, the sectioning of these nerves increased the amount of urine; stimulation of their peripheral ends causes formation of urine to stop. In animals with explanted kidneys deprived of their nerve supply, diuresis lasts for some days (Bieter). In addition, it was shown by Burton-Opitz and Lucas, that section of the splanchnic nerves increases renal blood flow, whereas stimulation of them decreases the flow. In the increased formation of urine following splanchnic section, it would seem likely that the glomeruli played a role. And, to be sure, direct observation of glomeruli of frogs during stimulation of the ipsolateral splanchnic nerve reveals cessation of blood flow through many of the glomeruli; approximately 50 per cent become inactive The afferent arterioles of such glomeruli become constricted. When the electrical stimulation is discontinued, the afferent arterioles suddenly dilate with a burst of blood flow Stimulation of the central ends of cut sciatic and vagus nerves produces similar responses Actual section of the splanchnic nerves, as expected, results in an increase in the number of active glomeruli corresponding to the increased amount of urine formed. The greater output of urine lasts for a short while until readjustments in glomerular circulation take place. Attempts to put this information to practical test by sympathetic nerve blocks have been made in cases of anuria due to hemoglobinuric (lower nephron) nephrosis, with variable results.

*Glomerular Permeability*

There is reason to believe that the walls of the glomerular capillaries behave as filters and that molecules below a certain size normally seep through the "pores" It is stated (Bott and Richards) that most of the mesh surface [illegible]

allows particles of 50 Ångstroms to go through. In other words, substances with a molecular weight of 68,000 or less pass through the glomerular filter For example, hemoglobin with a molecular weight of 68,000, egg albumin (molecular weight 35,000), Bence-Jones protein (molecular weight 20,000 to 30,000) and myoglobin (molecular weight 17,500) are excreted, whereas serum albumin (molecular weight 70,000), serum globulin (molecular weight 156,000) and hemocyanin (molecular weight 5,000,000) are normally retained However, the sizes of the "pores" cannot be the entire factor determining the size of the molecules excreted; actually, there is currently being accumulated evidence that small amounts of protein*, albumin especially, but also globulins and even fibrinogen, may normally pass the glomerular filter, subsequently to be reabsorbed by the proximal tubules It is suggested (Addis) that, ordinarily, normal capillaries allow at least 5 mg of protein per 100 cc of blood to escape through their walls and that the glomerular capillaries are probably equally permeable If, then, this minimal amount of 5 mg of protein passed the glomerular filter, it would yield 9 Gm of protein in the urine unless it were reabsorbed

The detection of such small amounts of protein by microchemical techniques is said not to be possible and that, for this reason, analysis of glomerular filtrate, aspirated directly from the nephron failed in the past to reveal the presence of protein Recently, Terry and his associates have found that they could produce proteinuria with albumin, globulin and fibrinogen in normal dogs, merely by raising the level of plasma proteins to about 9 6 Gm per cent They termed this level the renal threshold for proteinuria. In other words, given a high enough blood level, protein of molecular weights many times 68,000 readily seep past the normal glomeruli of dogs

Under *abnormal conditions*, the glomerular filtration is affected by changes within the walls and lumens of the glomerular capillaries Glomerular stasis, embolization and thrombosis, inflammatory and degenerative alterations all may contribute a vector to disturbed glomerular filtration This may occur not only by direct organic modification of the capillary walls, and, hence the permeability, but by interference with the glomerular circulation through stenosis, or by dilatation of the glomerular capillaries or arterioles. In many diseases, the interferences are of a focal, variable or even functionally neutralizing nature, involving individual capillaries (as in diabetic glomerulosclerosis, for example) so as to hinder or to make impossible the detection of their influence and localization by clearance studies.

It is further obvious that stagnation of the blood in the glomerular capillaries, as in congestive heart failure, is a hindrance to effective filtration because of the simple fact that inadequate blood is exposed to the surface of the glomerular filter However, there is another matter to be considered which is probably important, but poorly understood, and that is the effect of the stagnation of blood on the functional integrity of the wall of the glomerular capillaries The answer to this problem has a direct pertinence to the state of the glomeruli in a variety of disorders including shock and glomerulonephritis The matter of altered permeability of glomerular capillaries following abnormal dilatation is an additional problem on which adequate precise data are lacking Dilatation of other capillaries with adrenalin has been shown by Krogh to result in their increased permeability to protein so that a similar situation might be expected to exist in glomerular capillaries In the lesion of diabetic glomerulosclerosis, the glomerular capillaries surrounding the lesion are often enormously dilated (Allen). It has been suggested that this conspicuous glomerular capillary dilatation may play a part in the loss of protein

*"Albuminuria" is commonly used incorrectly in place of "proteinuria", the latter may involve not only albumin, but also globulins, fibrinogen, nucleoprotein and proteoses.

alkalosis, is not to be regarded necessarily as the histologic cause of the disturbance in tubular control of pH, as has been done

*Renin Formation*

An additional function of the tubules appears to be the formation of renin, particularly in ischemic kidneys, or in kidneys with reduced renal pulse pressure. Whether or not the tubules are concerned in the hypertensive mechanism by the production of certain aldehydes, the elaboration of enzymes, or the deamination of pressor amines remains to be more conclusively demonstrated

*Influence of Hormones on Renal Function*

Facts on the precise individual and correlated influence of hormones on renal function are only beginning to be accumulated. Thyroid extract has a diuretic action on normal subjects usually through its influence on general metabolic processes rather than by control of renal function, although its antagonism to the antidiuretic pituitary hormone has been suggested The antidiuretic effect of posterior pituitary extract (pitressin) in patients with diabetes insipidus, whose urinary output may exceed 20 liters per day following damage to the posterior lobe, is well known. Small doses of the extract may produce such an antidiuretic effect that it is thought that the action may be due not to vasoconstriction but to action on the epithelium of the renal tubules. The growth hormone of the anterior pituitary gland markedly improves the renal function (PAH and inulin clearances) that had been previously depressed in hypophysectomized dogs (White et al.).

The role of the adrenal cortex in controlling the excretion of sodium and potassium is also recognized as is that of the parathyroid glands in the renal regulation of the levels of phosphates and calcium, and the elimination of water. Polyuria is a common symptom of hyperparathyroidism However, it is the integrated role of the hormones in the "general adaptation syndrome" that has commanded recent interest. It appears to have been shown by Selye that the administration of adrenocorticotropic hormone (ACTH) or desoxycorticosterone acetate (DCA), especially in animals prepared by unilateral nephrectomy, high sodium diet and certain types of stress (for example, cold) results in the production of lesions of benign and malignant nephrosclerosis, and of periarteritis nodosa. These phenomena may be inhibited by the use of acidifying salts, such as ammonium chloride.

There is no satisfactory evidence that Addison's disease produces any significantly consistent morphologic changes in the kidneys. Whatever impairment of renal function occurs in Addison's disease is secondary to shock, dehydration, and hypervolemia. Between crises, the renal function is not impaired except for some diminution of the rate of glomerular filtration, and some interference with tubular excretion of potassium and reabsorption of water and sodium These disturbances, which are corrected by specific therapy, present no serious problem except in addisonian crises.

*Tubular Reabsorption*

Normally glucose and bicarbonate are reabsorbed completely; sodium, chloride, and calcium are reabsorbed except for a small fraction of 1 to 2 per cent; about 8 per cent of the filtered potassium and about 20 per cent of the uric acid are excreted. The excreted fractions of phosphate and urea are about 45 per cent and 60 per cent, and of creatinine somewhere around 70 per cent.

Much remains to be learned about the role of tubular enzymes in the process of reabsorption and excretion For example, alkaline phosphatase in the epithelium of the proximal convoluted tubules hydrolyzes organic hexosephosphate with the liberation of glucose to the peritubular capillaries, after preliminary phosphorylation of the glucose Presumably a similar mechanism for the reabsorption of glucose with the aid of phosphatase obtains in the intestinal tract In connection with the phosphatases, the early data dealing with the precise types and localization of the phosphatases in various parts of the nephrons to the exclusion of others need to be modified. Standard incubation periods of enzyme and substrate at standard pH may fail to reveal existing phosphatases Some of the cells, or

some components of cells, require longer incubation than others to demonstrate their content of enzyme by Gomori's method or a modification of it (Gomori, Newman et al ). With such variation in pH and time of incubation, alkaline, as well as acid phosphatase may be demonstrated in both the proximal and distal portions of the nephron; in addition, phosphatases are present in the basement membranes and brush border of the proximal tubules, in the endothelial cells and media of blood vessels, and even in the stromal nuclei Awareness of the many inhibitors of phosphatase, including cyanide, bile salts, amino acids, heat, and mechanical interferences, is important in the accurate evaluation of this group of enzymes in histologic sections

## Clearance

The term *clearance* was orginally used in 1928 by Møller, McIntosh and Van Slyke to refer to the volume of blood cleared of urea by one minute's excretion of urine This volume is equal to $\frac{U}{P}V$, where U and P equal the concentration of urea in the urine and plasma respectively, and V equals the cubic centimeters of urine excreted per minute Since then, clearance studies have been applied to a wide range of other substances, including creatinine, diodrast, para-aminohippurate, inulin, phenol red, phosphate, sulfate, amino acids, penicillin, aureomycin, and radioisotopes (e g , $Na^{24}$) By the use of one or other of these agents, it is said to be possible to measure glomerular filtration rate, filtration fraction, renal blood flow, and maximal tubular function

Of all the clearance tests, the urea studies are a particularly sensitive index of renal function, and the most dependably revealing from the point of view of clinical application Urea clearance tests reflect renal insufficiency earlier than other renal function tests However, no one test is entirely adequate to disclose all components of renal dysfunction The average maximal urea clearance is about 75 cc per minute (that is, for urinary excretion of more than 2 cc per minute) Most observers state that it is not until the urea clearance is about 40 per cent of normal that the concentration of blood urea as well as of creatinine become elevated Goldring and Chasis, however, insist that there is a complete linear correlation between the level of azotemia and the degree of urea clearance They believe that this correlation is often hidden by extrarenal factors, such as protein intake. For this reason, the statement that urea clearance must be reduced to 40 per cent of normal before azotemia occurs, represents a misconception according to them.

### *Principles of Clearance Studies*

By interpolating the values of glomerular filtration, tubular reabsorption, and tubular excretion of certain substances, estimates can be made of several features of renal dynamics. These are (1) the volume of glomerular filtrate per unit of time, or filtration rate, (2) the filtration fraction, (3) the rate of renal blood flow and (4) the maximal tubular function

With the use of a substance such as inulin, clearance values equal those of the *glomerular filtrate* This is so because the inulin passes the glomerular filter in the same concentration as it exists in the plasma and is neither reabsorbed nor excreted by the tubules The inulin clearance is determined by the standard formula $\frac{U}{P}V$ The normal clearance is 120 to 130 cc per minute and, as stated, measures the rate of formation of glomerular filtrate. The normal maximal urea clearance is less (75 cc ) because, unlike inulin, a certain amount of urea is returned to the plasma by the mechanism of tubular reabsorption This figure actually signifies that the amount of urea excreted in the urine in one minute is that contained in 75 cc. of plasma The formula $\frac{U}{P}V$ applies for urea clearance when more than 2 cc of urine are excreted per minute, if the amount is under 2 cc the formula is $\frac{U}{P}\sqrt{V}$, the normal value of which is 54 cc This dependence of clearance values on the volume of urine applies to the clearance value of urea, but not to the other substances used. This is so because the amount of tubular reabsorption of water determines the volume of urine ex-

creted, and the amount of urea that diffuses back through the tubules is dependent on its concentration in the tubular lumen. This is not the case with inulin, diodrast and other commonly used agents

There are additional substances which not only are filtered through the glomeruli but are also excreted by the tubules. Phenol red, phenolsulfonphthalein, para-aminohippuric acid and diodrast are examples of such substances Diodrast undergoes complete clearance from the blood during one circulation through the kidney Hence the diodrast clearance is a measure of *renal blood flow* The maximal capacity of the tubules to excrete diodrast when the plasma is saturated with this, or a similarly behaving substance is regarded as an index of the total functioning tubular mass (Tm) The Tm would, of course, differ for each substance used

As would be anticipated, the normal plasma clearance of substances such as creatinine (175 cc ), phenol red (400 cc ) and diodrast (697 cc ) is greater than the clearance of urea (75 cc ) and inulin (125 cc ) The reason is that to the *amount of creatinine, phenol red, and diodrast* filtered through the glomeruli, there is added an additional increment to the filtrate by the process of tubular excretion No tubular excretion of urea or inulin occurs, on the contrary, some tubular reabsorption (about 40 to 50 per cent—Herrin) of urea takes place so that its clearance is less than that of unresorbed inulin By the same mechanism, it could be guessed that the clearance of glucose at normal plasma concentrations is zero inasmuch as at such levels glucose is completely reabsorbed and returned to the plasma However, by increasing the concentration of glucose to high levels, the tubular capacity to reabsorb this substance is saturated, so that at such times, the excess glucose in the glomerular filtrate is excreted and the glucose clearance then equals the inulin clearance This phenomenon of tubular saturation may occur for other substances, for example, it may occur for hemoglobin when the tubular epithelium becomes packed with it or hemosiderin, as in paroxysmal hemoglobinuria (plate 124). The clearance value of glucose when the reabsorptive capacity of the tubules is saturated is a measure of the maximal rate of tubular reabsorption (for glucose) This value is called glucose Tm and is 320 mg per minute when the plasma level of glucose has been raised from 200 to 800 mg per cent

A similar process of thought has been applied to the maximal excretion of diodrast and other substances similarly excreted by the tubules, for example, creatinine and phenol red For these substances there is a maximal quantity which can be handled by the cells of the tubules per unit of time Therefore, when the plasma concentration is raised above a critical level, the tubular excretory mechanism is fully taxed and the substance is excreted at a maximal rate. This value for diodrast, for example, is the diodrast Tm and is presumed to measure the total quantity of tubular excretory tissue This tissue is assumed to be the total quantity of intact proximal tubules inasmuch as these are the tubules which are thought to excrete diodrast (as well as creatinine and phenol red). The ratio $\frac{\text{inulin clearance}}{\text{diodrast clearance}}$ is equal to $\frac{\text{filtration rate}}{\text{renal plasma flow}}$. *This ratio is equal to the fraction* of plasma filtered through the glomeruli and hence is called the filtration fraction (F.F.)

### *Limitations of Clearance Studies*

It is apparent that many of the determinations of the renal functions of even normal subjects (table 2) are characterized by an impressively wide variability. This deviation from the mean is hardly any less striking in statistical samples of clearance studies (e g, Earle) purporting to show the pattern of renal functions of diseased kidneys (table 3). It should be mentioned that even when the standard deviation or probable error is indicated on infrequent occasions, the further logical step of calculation of the statistical significance of the means from these data (chi square test, for example) is rarely carried out This is a basic computation that might well dampen the definiteness of many of the conclusions However, an impression of the extent of the variations is acquired from the data on 7 patients in the nephrotic stage of chronic glomerulonephritis with filtration rates vary-

ng from 11 to 73 per cent of normal (Earle). In 14 patients with acute glomerulonephritis, the filtration rate averaged 55 per cent of normal with a range of 25 to 92 per cent, while the tubular mass averaged 70 per cent of course been aware of many of the limitations Smith (1941) anticipated criticism of the use of these methods for the interpretation of the physiologic and morphologic status, particularly of *diseased* kidneys He acknowl-

TABLE 2 —*Mean Values for Renal Function in Normal Subjects (According to Goldring and Chasis)*

| | Males | Females |
|---|---|---|
| Rate of glomerular filtration ($C_{In}$, inulin clearance, cc /min ) | 131 ± 21.5 | 117 ± 15.6 |
| Effective renal plasma flow ($C_D$, diodrast clearance, cc /min ) | 697 ± 135.9 | 594 ± 102.4 |
| Maximal tubular excretory capacity ($Tm_D$, diodrast Tm, mg iodine/min ) | 51.8 ± 8.73 | 42.6 ± 9.46 |
| Maximal tubular resorptive capacity ($Tm_G$, glucose Tm, mg glucose/min.) | 375 ± 79.7 | 303 ± 55.3 |
| Filtration fraction $\left(\frac{C_{In}}{C_D}\right)$ % | 19 ± 0.02 | 20 ± 0.03 |
| $\frac{\text{Effective renal plasma flow}}{\text{Maximal tubular excretory capacity}}$ $\frac{C_D}{Tm_D}$ | 14.0 ± 2.16 | 14.2 ± 2.36 |
| $\frac{\text{Rate of glomerular filtration}}{\text{Maximal tubular excretory capacity}}$ $\frac{C_{In}}{Tm_D}$ | 2.63 ± 0.31 | 2.81 ± 0.56 |

TABLE 3 —*Values for Renal Functions in Subjects with Abnormal Kidneys (Earle)*

Renal functions in nephrotic edema

| | F E ♂ | S Y ♂ | S N ♂ | | G R ♂ | N I ♂ |
|---|---|---|---|---|---|---|
| | "Nephrotic glomerulo-nephritis" | Amyloidosis | "Nephrosis" | Healed 5 yrs. later | Heart failure | Acute glomerulo-nephritis |
| Filtration rate, cc /min (F R) | 25 | 45 | 125 | 122 | 54 | 33 |
| Renal plasma flow, cc /min (R P F) | 173 | 397 | 708 | 679 | 137 | 458 |
| Filtration fraction, % (F F) | 14 | 11 | 18 | 18 | 39 | 7 |
| Tm P A H, mg /min | 14 | 20 | 96 | 90 | — | 34 |
| Tm glucose, mg /min (Tmg) | 179 | — | — | — | — | — |
| Urea clearance, % normal | — | — | 148 | — | 64 | 29 |

| | Essential Hypertension ♀ | Lupus Erythematosus ♀ | Diabetic Glomerulosclerosis ♀ | Chronic Glomerulonephritis ♀ |
|---|---|---|---|---|
| F R | 60 | 42 | 40 | 43 |
| R P F | 277 | 698 | 199 | 262 |
| F F | 22 | 6 | 20 | 17 |
| Tm P A H | 38 | — | 32 | 41 |
| Tm glucose | — | 262 | 131 | — |
| Urea clearance | — | — | — | 30 |

normal with a range of 36 to 128 per cent. At least one of his patients with a "definite chronic nephritis" had a normal functional pattern as revealed by clearance studies Such variation is further emphasized by contrasting the data on similar conditions originating in other leading laboratories

Those engaged in clearance studies have of

edged that the glomerular permeability to inulin may be diminished without proportionally retarding the filtration of water, and that diseased tubules might allow water to escape to the exclusion of inulin, without in either case, having the differential changes detected The observation that similar clearance values can be obtained by the use of a

substance with a molecule smaller than that of inulin only partially reduces this limitation After all, to find, as Raaschow has, that inulin clearance may be markedly reduced in pyelonephritis, with histologically intact glomeruli, or that the urea clearance may be markedly reduced with infections and jaundice *in the presence of histologically normal* glomeruli (Hayman et al ), or that there are significant discrepancies between the renal blood flow calculated by clearance tests and that measured directly (Selkurt), raises some doubt as to the validity of the use of these methods as a measure of glomerular filtration in diseased kidneys or in diseased states

The recorded frequency of such discrepancies is less important than the fact that the neat correlation between physiologic and morphologic data can be completely disrupted for the reason that function has been altered by *structural change in ways that need to be* known, but obviously are not The glomerular filtrate of some nephrons may never reach the collecting tubules because it has escaped into the interstitial fluid or has been otherwise diverted. Such losses distort the clearance values And yet, it is just this mode of loss of filtrate that, on the one hand, has been postulated as occurring in hemoglobinuric (lower nephron) nephrosis, and, on the other, is found to be awkward and hence is disregarded in drawing conclusions (Earle[a]) from the clearance studies

In addition, all would agree with Smith that the presence of inert tissue should not distort the ratio $C_D/TmD$ However, if the tissue is not quite inert, but is functional in varying degrees as a result of renal structural disease, can it properly be assumed that the altered *tubules reabsorb and excrete in the* qualitative manner of normal tubules? It is wisely noted (Shannon, 1939) that from the standpoint of comparative physiology, the mechanisms for tubular excretion become more important in those species characterized by poor glomerular development, becoming paramount in those that are completely aglomerular Is it therefore not entirely reasonable to suggest that with conspicuous changes in glomerular as well as tubular structure, the test substances may be handled by glomeruli, tubules and capillaries in a manner different from that in which they are handled normally?

Furthermore, the value for maximal tubular function (Tm) is said "under ordinary circumstances" to be independent of changes in glomerular filtration rate (Earle[a]). Nevertheless, as Earle points out, "the large and acute variations (caused by administration of fluid) during the procedure render interpretation of the relationships quite unsatisfactory at times " *It is appreciated also that there may be difficulties* in achieving saturation of blood for the measurement of Tm's in the presence of greatly reduced values of filtration rate and renal plasma flow, especially when tubular function has not been seriously impaired. There is the additional possibility that the administration of large amounts of material *for measuring Tm's may cause renal vasoconstriction* Moreover, it is a recognized fact that diminished capacity of the tubule to concentrate urine and to form ammonia may occur without reflection of that impairment in the values of TmPAH or in Tm glucose

When the renal extraction ratio is low, there is admittedly great danger of reaching erroneous conclusions *in the study of most* renal diseases (Earle[a], 1950). [This ratio is determined with the use of blood collected from the renal vein by catheterization (Warren et al.) ] It is known that low renal extraction ratios of clearance substances occur in cases of advanced renal diseases, for example, benign nephrosclerosis and chronic glomerulonephritis (Bradley et al., Cargill). Clearly, this represents a serious limitation to the method and invalidates many of the findings of past *investigations by clearance studies and* perhaps helps to explain many of the contradictions.

While acknowledging the resourcefulness of the investigators of the clearance studies, we must avoid the error of using an exact measurement to define the limits of function of a structure, when that datum represents merely an algebraic composite of various degrees of functions of structures in various states of morphologic preservation. As Oliver forcefully

emphasizes (1950), such a composite may include many basically different functional and morphologic components, more or less individually modified by pathologic processes. It appears to be a practical fact that technically advanced clearance studies generally offer no greater practical revelation concerning prognosis and diagnosis of renal disease than can be learned by simpler tests The clearance tests, after all, are not measures merely of renal function but of many ancillary functions related to water, electrolyte and hormonal balance, through which the entire body influences the excretion of urine As others have pointed out, if these extrarenal functions are assumed to be quite normal, then the clearance tests may be considered measurements strictly of renal function The fact is that such an assumption is often not warranted clinically As one example, in congestive heart failure, the glomerular filtration rate is about two-thirds of normal (66 8 cc /min ) and the renal plasma flow is approximately one-third of normal (191 5 cc/min ) Inasmuch as myocardial failure of some degree occurs in many renal diseases including even acute diffuse glomerulonephritis (LaDue), it is obvious that the extrarenal factors can influence appreciably the figures of renal clearance, and, therefore, deflect accurate interpretation of the structural disorders of the kidneys To paraphrase Addis, it is not enough to know what the kidney is doing in terms of arithmetical summations of functions; for diagnostic, prognostic and therapeutic reasons it is essential to know the component factors that are at fault

In summary, the limitations of the more elaborate clearance tests on the kidneys with appreciable structural damage are imposed by the several conditions mentioned, as well as by the fact that the physiologic influences of such organic damage are often not in the same cumulative direction In other words, abnormal function may be camouflaged by an algebraic summation of two or more disturbed physiologic processes, for example, glomerular, tubular and prerenal, so that the final measurement of the derangement may be even a normal value

In *normal* subjects, it is theoretically possible that the functions of individual renal components may indeed be estimated with these astutely contrived clearance tests Even in such instances, the variability of the results is considerable However, in kidneys with characteristically variegated morphologic damage, not only from one nephron to the next, but even within a small segment of a nephron, the determination of filtration rates, filtration fractions, effective renal blood flow, and tubular excretory and secretory capacity—no matter how meticulously performed—are fraught with masked, obscurely neutralizing, as well as additive renal activities By no phrase is it meant that this method of study of renal function is without considerable use, it should be stressed, however, that interpretations of the tests on structurally damaged kidneys have often been unjustified and without adequate regard for the correlative morphologic changes Undoubtedly, future integrative refinements of method will reduce the limitations of the tests In the meantime, there is nothing to be gained by a blanket subordination of histologic data to arbitrary structural inferences based on the clearance studies

## Renal Function in Infants

As McCance has aptly demonstrated, the differences in renal function in the newborn and in adults are of a quantitative rather than qualitative nature There is a reduction in the clearance of most test substances, especially of those that are cleared by glomerular filtration The urine of the infant, and more particularly of the fetus, is less concentrated than that of the adult Possibly these features are dependent on the incomplete development of the loops of Henle, and on the prominent visceral epithelial cells of the glomerular tuft serving as a barrier to filtration In addition, the subcapsular glomeruli are usually immature at term (plate 5 B) At any rate, the practical point is that the functional flexibility of the kidneys of the newborn is limited, and their adaptability to acidosis, dehydration, surgical procedures, and other stresses is correspondingly limited. This type of narrow

reserve in infants is, of course, not unique with the kidneys, but is common to other organs

### Casts

Casts are visible in histologic sections of the kidney as well as in the urine The casts are classified as: (1) hyaline, (2) epithelial, (3) granular, (4) waxy, (5) cylindroids, (6) broad renal failure casts, (7) blood casts, (8) bile casts, (9) melanin casts, (10) calcium casts, (11) uric acid casts Casts are rarely found in the proximal portion of the nephron, they begin to form at the level of the distal convoluted tubules The reasons for this are, first, that the glomerular filtrate is almost always insufficiently concentrated to form casts until it reaches the distal nephron Secondly, the rate of flow of the glomerular filtrate is about 100 times greater than that in the collecting tubules (Addis) and is therefore too rapid for the accumulation of casts Undoubtedly additional factors, such as oliguria, pH, and isoelectric point play a role in their formation. Casts tend to disintegrate in the urine so that examination for them should be made with recently passed samples. This is particularly true of urine that is alkaline when passed or that is made alkaline by the bacterial decomposition of urea with the resultant formation of ammonia

#### *Hyaline Casts*

Hyaline casts are gels soluble in water (Addis) and in dilute acetic acid, formed by a combination of protein and sulfur-containing polysaccharide Chemical analysis of hyaline casts (Addis) reveals them to be composed of

$$C = 48.6\%$$
$$H = 2.4\%$$
$$N = 11.3\%$$
$$S = 2.6\%$$

length and 10 to 50 microns in thickness Often granular fragments of epithelium, fat droplets, and blood are admixed with the sticky hyaline cast Occasional hyaline casts may be incidental findings in sections of kidneys or they may be numerous as in renal amyloidosis (plate 25 E). As a rule, these casts provoke no tubular reaction, although postmortem desquamation of epithelium may simulate degenerative change. In some instances of renal reaction to sulfonamides, these casts are associated with prominent giant cell granulomas and thrombophlebitis of adjacent interlobular or arcuate veins (plate 143, 144A). In sections of myeloma nephrosis, the casts are accompanied by a characteristic syncytium of tubular cells (giant cells) (plate 150). The damage wrought or reflected by hyaline casts, as with other types of casts, is to be judged in sections by their number and density; their presence in isolated foci in sections, or in small numbers in the urine, is not clinically meaningful. Hyaline casts may be found in large numbers in the urine in most instances of albuminuria. They may be present in large numbers in cases of chronic passive congestion, during recovery from acute glomerulonephritis even after albuminuria has disappeared, prior to the onset of diabetic coma, and in cases of jaundice (Fishberg).

#### *Epithelial Casts*

Cylindroids resemble hyaline casts qualitatively, but are longer and taper to a point at either end They are found in more or less the same conditions as are hyaline casts. Because cylindroids may be found in the urine associated with inflammatory conditions of the urinary tract distal to the kidney, it is thought some cylindroids may not originate in the kidney but represent mucoid products of inflammation The epithelial casts are formed from desquamated tubular epithelial cells or granular fragments of them Epithelial casts may be combined with hyaline casts The fragments may contain lipid hemosiderin, bile or melanin and thereby furnish clinically important information. For example, hemosiderin granules are suggestive of abundant hemolysis as in nocturnal hemoglobinuric nephrosis, the lipid granules, especially if birefringent, are indicative of the nephrotic syndrome or of the several other conditions in which the tubular epithelium may be laden with fat, e g., diabetes mellitus, phosphorus or carbon tetrachloride poisoning (plate 66 C,

TABLE 4.—*Normal Values of Relative Concentration of Substances in Urine and Blood (Fishberg)*

| | Concentration in urine mg % | Concentration in blood mg % | Concentration ratio | Concentration in blood in renal insuffic |
|---|---|---|---|---|
| Urea | 2000 | 30 | 66 6 | Increased |
| Uric acid | 60 | 2 | 30 | Increased |
| Creatinine | 75 | 2 | 37 5 | Increased |
| Indican | 1 | 0 05 | 20 | Increased |
| Phosphate | 150 | 3 | 50 | Increased |
| Sulfate | 150 | 3 | 50 | Increased |
| Potassium | 150 | 20 | 7 5 | Slight increase |
| Chloride | 500 | 350 | 1 4 | No increase |
| Sodium | 350 | 335 | 1 | No increase |
| Calcium | 15 | 10 | 1 5 | No increase |

75, 107) Addis believed that the *granular* and *waxy* casts were progressive stages of autolytic transformation of the epithelial casts The waxy cast (which, of course, has no reference to the waxy or amyloid kidney) forms after prolonged stasis (anuria) in a given nephron The autolysis of the epithelial cast may occur in the urine within the bladder (Addis) Of particular interest are the *broad renal failure casts* (plate 71) These are epithelial, granular or waxy casts which have stagnated in the collecting tubules and ducts of Bellini and, in large numbers, they are indicative of severe oliguria or anuria when observed in histologic sections

### *Pigment Casts*

Pigment casts are currently the source of much discussion and speculation, particularly with regard to their functional significance The casts of hemoglobin and myoglobin—and often the casts of bile—are indistinguishable by routine methods of staining paraffin or frozen sections of tissue Spectroscopic methods may soon be applicable to their differentiation in sections The benzidine-hydrogen peroxide stains are unreliable in their identification of hemoglobin versus bile Hemoglobin casts resulting from laking of red blood cells already within the tubular lumens must be distinguished from hemoglobin casts produced by hemoglobinemia The casts themselves may look alike, although in the case of hematuria, some intact red blood cells may be included within the casts (plate 130) Contrary to standard impressions obtained from the literature, the tubular epithelium about casts of hemoglobin may be—and usually is—histologically intact (plate 128, 130) Isolated hemoglobin casts are commonly present in a loop of the distal convoluted tubule in the vicinity of the glomeruli in many conditions, especially in infectious diseases In hemoglobinuric nephrosis, these casts are predominant in the collecting tubules of the medulla (plate 128).

Bile casts are often greener than hemoglobin casts but may look alike in routine paraffin sections stained with hematoxylin and eosin The tubular epithelial reaction to bile is similar to that of other pigments including hemoglobin, myoglobin and melanin (plate 133, 134, 328). The bile casts are located similarly to the hemoglobin casts. Renal casts of melanin are pathognomonic of the existence of malignant melanoma They are found in the distal tubules (plate 125) and are of no renal functional significance

Calcium casts are formed by agglutinated concretions of desquamated, calcium encrusted epithelium, in practically all instances from the distal tubules These casts occur in association with alkalosis, lesions of bone, hyperparathyroidism, and idiopathic hypercalciuria. They are usually of little consequence, unless they occur in critical locations, as in the apex of the pyramids where they may exert serious obstructive effects (plate 197)

Uric acid, or urate casts, are composed of crystals formed physiologically in the newborn, in gout or in leukemia following therapeutic destruction of nuclear material They do not compromise renal function except in certain instances of gout (plates 154, 155) Further discussion of the casts is included in the sections dealing with the individual diseases

TABLE 5.—*Normal Volume of Urine (Kolmer and Boerner)*

| Age | cc per 24 hours |
|---|---|
| 1 to 2 days | 15 to 60 |
| 3 to 10 days | 100 to 300 |
| 10 days to 2 months | 250 to 450 |
| 2 months to 1 year | 400 to 500 |
| 1 to 3 years | 500 to 600 |
| 4 to 8 years | 600 to 1000 |
| 9 to 15 years | 800 to 1400 |
| Over 15 years | 1000 to 1600 |

TABLE 6.—*Normal Constituents of Urine (Grams per 24 hours)*

| | |
|---|---|
| Total solids | 60–70 Gm |
| Titratable acidity | 200–500 cc N/10 alkali |
| Potassium (as $K_2O$) | 2 0–2 5 Gm |
| Calcium | 0 1–0 3 Gm |
| Total sulfur (as $SO_3$) | 1 5–2 Gm |
| Magnesium (as MgO) | 0 2 Gm |
| Chloride (as NaCl) | 5–15 Gm |
| Phosphorus | 2–4 Gm |
| Sodium (as $Na_2O$) | 4 0–4 5 Gm. |
| Iron | 0 003 Gm |
| Reducing substances | 0 5–1 5 Gm |
| *Total nitrogen* | *8–18 Gm* |
| Urea | 12–30 Gm |
| Amino acids | 0 1–0 15 Gm. |
| Ammonia | 0 6 Gm |
| Uric Acid | 0 4–0 7 Gm |
| Creatinine | 1 5 Gm |
| Urobilinogen | 1–5 Ehrlich units |
| Gonadotropin | |
| Men | 26-105 mouse units |
| Women | 13-105 mouse units |
| 17-ketosteroid excretion | |
| Men | 7–14 mg |
| Women | 4–11 mg |
| Children | <1 mg |

Traces of the following organic substances are also present
pigments, sugar (2–3 mg per cent), fatty acids, carbonates, diastase, and mucinous compounds

## SUMMARY OF REPRESENTATIVE RENAL FUNCTION TESTS

*Phenolsulfonphthalein Test*

| *Intravenous* | | *Intramuscular* | |
|---|---|---|---|
| First 15 minutes | 25–50% | First hour | 40–60% |
| Second 15 minutes | 15–25% | Second hour | 20–25% |
| *Average total in 30 minutes* | 50% | *Total* | *60–85%* |
| Second 30 minutes | 10–15% | | |
| Total, 60 minutes | 60–65% | | |
| 120 minutes | 70% | | |

The appearance of the dye may be delayed by ether or any deep anesthesia. Advantages in fractionation of the data are conceded.

*Urea Clearance*
Maximal: 75 cc. of plasma cleared per minute (100%).
Standard: 54 cc. of plasma cleared per minute (100%).

*Inulin Clearance*
120–130 cc of plasma cleared per minute.

*Creatinine Clearance*
175 cc. of plasma cleared per minute

*Diodrast Clearance*
700 cc of plasma cleared per minute.

*Fishberg's Concentration Test*
In at least one specimen the specific gravity is greater than 1 022 and often reaches 1.032

*Fishberg's Dilution Test*
1200 cc. of water drunk within ½ hour are normally eliminated in less than 3 hours and the specific gravity of the largest specimen is about 1 002.

*Volhard's Dilution-Concentration Test*
About 1500 cc of urine are excreted within 4 hours after 1500 cc of fluid are drunk The specific gravity is lowered to 1 002 After withholding fluids, the specific gravity normally rises to about 1 030

*Concentration Tests of Addis and Shevky*
The specific gravity of the urine reaches 1 026 to 1 032 after abstinence from fluids for 24 hours. [Note Several substances in the urine may elevate the specific gravity without reflecting the ability of the kidney to concentrate. Diodrast, albumin

(Albarran) ]

The normal range of the specific gravity of the urine spans at least 0 010 The volume of urine formed in the 12 hour night period is about 400 cc., with a specific gravity of approximately 1 018 The volume of the 12 hour day period is about two to three times as great. Factors such as fluid intake, weather, exercise, etc , obviously modify these values. The capacity to concentrate the urine is indicated by the terms, originally suggested by von Korányi, hypersthenuria, isosthenuria, and

hyposthenuria The designation "hyposthenuria" was based on the determinations of freezing points of the urine. Inasmuch as the freezing point is an indication of the number of particles in solution, it is more or less a measure of the specific gravity, notwithstanding the fact that large protein molecules may have a disproportionately greater effect on the specific gravity than on the freezing point Hence, these terms are now used to indicate the range of specific gravity of the urine In hyposthenuria the patient is unable to concentrate the urine and its specific gravity remains below 1 010, while the freezing point, incidentally, is close to that of blood, i e, −0 56° C In patients with isosthenuria, the specific gravity of the urine stays at 1 010, which is the specific gravity of the glomerular filtrate, or plasma minus the proteins In renal disease, both hyposthenuria and isosthenuria are evidences of the inability of the kidney to concentrate urine, and therefore of severe impairment The low specific gravity of the urine in diabetes insipidus, for example, is another matter altogether, since the urine of such patients can be made more concentrated with extract of posterior pituitary gland

### Addis Count

The Addis Count refers to the elements concentrated in the urinary sediment excreted during a 24-hour period, during which the patient has taken no fluid The sediment is examined unstained in a blood counting chamber and separate counts are made of (1) the red blood cells, (2) epithelial and white blood cells combined and (3) the casts The average counts of these elements for a normal person per 24-hour period are:

(1) Red blood cells. 130,000
(2) Epithelial and white blood cells: 650,000
(3) Casts. 2,000
(4) Protein: 10 mg

These counts are modified by exercise and various pathologic states The general attitude toward this procedure is that it is useful in investigative studies but not practical as a routine method Hence, it has not achieved widespread used Certainly, Addis, his associates, and others have made interesting, informative, and practical use of the method which is not nearly as complicated, nor as time-consuming, as it is commonly thought to be.

### References


Addis, T Glomerular Nephritis Diagnosis and Treatment New York, Macmillan, 1948

——, and Oliver, J The Renal Lesion in Bright's Disease New York, Paul B Hoeber, 1931

Albarron, J Exploration des fonctions rénales. Paris, Masson et Cie, 1905

Allen, A C So-called intercapillary glomerulosclerosis—a lesion associated with diabetes mellitus morphogenesis and significance Arch Path 32: 33-51, 1941

Allen, F M Arterial hypertension J A M A 74, 652-655, 1920

Alving, A S, and Van Slyke, D D Significance of concentration and dilution tests in Bright's disease J Clin Invest 13: 969-998, 1934

Bieter, R N The effects of the splanchnics upon the glomerular blood flow in the frog's kidney Am J Physiol 91: 436-456, 1930

Bensley, R R The efferent vessels of the renal glomeruli of mammals as a mechanism for the control of glomerular activity and pressure Am. J Anat 44: 141-169, 1929

——, and Steen, W B Functions of the differentiated segments of the uriniferous tubules Am J. Anat 41: 75-96, 1928

Berglund, H, Medes, G, Huber, G C, Longcope, W T, and Richards, A N The Kidney in Health and Disease Philadelphia, Lea and Febiger, 1935

Binger, M W, and Keith, N. M The effect of diuretics in different types of edema J A M A 101: 2009-2016, 1933

Bott, P A, and Richards, A N The passage of protein molecules through the glomerular membranes J Biol Chem 141: 291-310, 1941

Bowman, W On the structure and use of the Malpighian bodies of the kidney with observations on the circulation through that gland Phil Tr Roy Soc London, 1842, Part I, p 57-80.

Bradley, S E, Curry, J J, and Bradley, G P Renal extraction of p-aminohippurate in normal subjects and in essential hypertension and chronic diffuse glomerulonephritis Federation Proc 6: 79, 1947

Burton-Opitz, R, and Lucas, D R. Ueber die Blutversorgung der Niere I Der einfluss der Erhöhung des Druckes in den Harnwegen sowie der Reizung und Durchschneidung der den Plexus renalis bildenden Nervfasern Pflüger's Arch f d ges Physiol 123: 553-595, 1908

Cannon, W B Organization for physiological homeostasis Physiol Rev 9: 399-431, 1929

Cargill, W H The measurement of glomerular and tubular plasma flow in the normal and diseased human kidney. J. Clin Invest 28: 533-538, 1949

COPE, C L Rational assessment of renal damage Lancet 2: 799–802, 1934

CUSHNY, A R The Secretion of Urine London and New York Longmans, Green, 1917

DARROW D C Body-fluid physiology the role of potassium in clinical disturbances of body water and electrolyte New England J Med 242: 1014–1018, 1950

DEGRAFF, A C, AND NADLER, J E Review of toxic manifestations of mercurial diuretics in man J. A M. A 119: 1006–1011, 1942

DIGGS, L W in Medical Physics Ed by Otto Glasser Vol II Chicago, The Year Book Publishers, 1950

EARLE, D P JR: Introduction to the study of renal function Am J. Med 9: 78–87, 1950

——: Renal function tests in the diagnosis of glomerular and tubular disease Bull New York Acad of Med 26: 47–65, 1950

EDWARDS, J G Functional sites and morphologic differentiation in renal tubule Anat Rec 55: 343–367, 1933

—— Renal unit in kidney of vertebrates Am J Anat 53: 55–87, 1933

FISHBERG, A M Hypertension and Nephritis 4th Ed Philadelphia, Lea and Febiger, 1939

FOLLIS, R H, JR, Orent-Keils, E, AND McCollum, E V The production of cardiac and renal lesions in rats by diet extremely deficient in potassium Am J Path 18. 29–39, 1942

GOLDRING, W, AND CHASIS, H Hypertension and Hypertensive Disease New York, The Commonwealth Fund, 1944

GOMORI, G Distribution of acid phosphatase in tissues under normal and under pathologic conditions Arch. Path 32: 189–199, 1941

GROLLMAN, A The combination of phenol red and proteins J Biol Chem 64: 141–160, 1925

GRUBER, C M The anatomic innervation of the genito urinary system Physiol Rev 13. 497–609, 1933

HAYMAN, J M, JR Estimations of afferent arteriole and glomerular capillary pressures in the frog kidney Am J Physiol 79: 389–409, 1927

——, MARTIN, J W, JR, AND MILLER, M Renal function and the number of glomeruli in the hu- [illegible] Arch Int Med 64: 60–83, 1939

—— .

HEF ,
function Physiol Rev 21: 529–562, 1941

HERRING, P T Histologic evidence of secretion by kidney tubules of the skate J Physiol 67: 42 (Proc ), 1929

HINMAN, F. Significance of renal counterbalance in surgical treatment of renal lesions particularly [illegible]lateral J A M A 94: 1207–1210, 1930

HUBER, G. C Morphology and structure of the mammalian renal tubule. Harvey Lectures, 1909–10, p 100–149.

—— On the morphology of the renal tubules of vertebrates. Anat. Rec 13: 305–339, 1917.

JAFFE, H L, MASTER, H L, AND DORRANCE, W.: The salt depletion syndrome following mercurial diuresis in elderly persons. Am. J M. Sc. 220: 60–65, 1950

JOLLIFFE, N, AND CHASIS, H: Filtration and secretion of exogenous creatinine in man Am J. Physiol 104: 677–680, 1933

KAHN, J R, SKEGGS, L T., AND SHUMWAY, N P.: Studies of the renal circulation. Circulation 1: 445–453, 1950.

KOLMER, J A., AND BOERNER, F: Approved Laboratory Technic, 4th Ed New York, D Appleton-Century Co, 1945

VON KORÁNYI, A: Physiologische und klinische Untersuchungen über den osmotischen Druck thierscher Flüssigkeiten. I and II, Ztschr f klin. Med 33: 1–54, 1897, 34: 1–52, 1898

KROGH, A The Anatomy and Physiology of Capillaries New Haven, Yale University Press, 1929, p 335

LADUE, J S Role of congestive heart failure in production of edema of acute glomerulonephritis. Ann Int Med 20: 405–422, 1944.

LEITER, L Nephrosis Medicine 10: 135–242, 1931

LONGCOPE, W T The pathogenesis of glomerular nephritis Bull Johns Hopkins Hosp 45: 335–360, 1929.

LOTSPEICH, W D Renal tubular reabsorption of chloride Am J Physiol. 148: 445–448, 1947.

LUDWIG, C Nieren und Harnbereitung Handwörterb d Physiol, Brnschwg 2: 628–640, 1850.

McCANCE, R A Renal function in early life Physiol. Rev 28: 331–348, 1948

—— Renal physiology in infancy Am J. Med 9: 229–241, 1950.

——, AND ROBINSON, J. R Evaluation of renal clearances. Proc. Roy Soc. Med 42: 475–480, 1949.

McFARLANE, D Experimental phosphate nephritis in the rat J Path & Bact 52: 17–24, 1941.

MARSHALL, E K, JR. The comparative physiology of the kidney in relation to theories of renal secretion Physiol Rev. 14. 133–159, 1934.

—— AND CRANE, M M Secretory function of renal tubules Am J. Physiol. 70: 465–488, 1924.

——, AND KOLLS, A C Studies on nervous control of the kidney in relation to diuresis and urinary secretion, I Effect of unilateral excision of adrenal, section of splanchnic nerves, and section of renal nerves on the secretion of the kidney Am J Physiol. 49: 302–325, 1919.

MAXWELL, M H, BREED, E. S., AND SMITH, H. W.: Significance of the renal juxtamedullary circulation Am J Med 9: 216–228, 1950

MILLIKAN, G A Muscle hemoglobin Physiol Rev. 19. 503–523, 1939

Møller, E., McIntosh, J. F., and Van Slyke, D. D. Studies of urea excretion. II. Relation between urine volume and the rate of urea excretion by normal adults. J. Clin. Investigation 6: 427–465, 1928.

Mudge, G. H., Foulks, J., and Gilman, A.: The renal excretion of potassium. Proc. Soc. Exper. Biol. & Med. 67: 545–547, 1948.

Newman, W., Feigin, I., Wolf, A. and Kabut, E. A.: Histochemical studies on tissue enzymes. IV. Distribution of some enzyme systems which liberate phosphate at pH 9.2 as determined with various substrates and inhibitors, demonstration of three groups of enzymes. Am. J. Path. 26: 257–306, 1950.

Oliver, J. When is the kidney not a kidney? J. Urol. 63: 373–402, 1950.

Oliver, J., and Lund, E. M. Cellular mechanisms of renal secretion, study by extravital method, structural phase of secretory mechanism. J. Exper. Med. 57: 435–458, 1933.

Peters, J. P. Role of sodium in the production of edema. New England J. Med. 239: 353–362, 1948.

Pitts, R. F. The renal regulation of acid base balance with special reference to the mechanism for acidifying the urine. Science 102: 49–54, 81–85, 1945.

——, and Alexander, R. S. The nature of the renal tubular mechanism for acidifying the urine. Am. J. Physiol. 144: 239–254, 1945.

——, Ayer, J. L. and Schiess, W. A. The renal regulation of acid base balance in man. III. The reabsorption and excretion of bicarbonate. J. Clin. Investigation 28: 35–44, 1949.

Poll, D., and Stern, J. E. Untoward effects of diuretics with special reference to mercurial diuretics. Arch. Int. Med. 58: 1087–1094, 1936.

Raaschou, F. Studies of Chronic Pyelonephritis with Special Reference to the Kidney Function. Copenhagen, Ejnar Munksgaard, 1948.

Reaser, P. B., and Burch, G. E. Radiosodium tracer studies in congestive heart failure. Proc. Soc. Exper. Biol. & Med. 63: 543–546, 1946.

Reubi, F. C., and Schroeder, H. Can vascular shunting be induced in the kidney by vasoactive drugs? J. Clin. Invest. 28: 114–123, 1949.

Rhoads, C. P., Van Slyke, D. D., Hiller, A., and Alving, A. S. Effects of novocainization and total section of nerves of renal pedicle on renal blood flow and function. Am. J. Physiol. 110: 392–398, 1934.

Richards, A. N. Nature and mode of regulation of glomerular function. Am. J. M. Sc. 170: 781–803, 1925.

—— Methods and Results of Direct Investigation of Kidney. Williams and Wilkins, Baltimore, 1929.

—— Recent developments in the experimental study of the function of the kidney (Abst.) Arch. Path. 13: 847–848, 1932.

—— Croonian Lecture, Processes of urine formation. Proc. Roy. Soc. London 126: 398–432, 1938.

——, and Schmidt, C. F. Description of glomerular circulation in frog's kidney and observations concerning action of adrenalin and various other substances upon it. Am. J. Physiol. 71: 178–208, 1924.

——, and Walker, A. M. Accessibility of glomerular vessels to fluid perfused through renal portal system of frog's kidney. Am. J. Physiol. 79: 419–432, 1927.

Selkurt, E. E. Comparison of renal clearances with direct renal blood flow under control conditions and following renal ischemia. Am. J. Physiol. 145: 376–386, 1946.

Selye, H. Textbook of Endocrinology, 2nd ed. Montreal, Acta Endocrinologica Inc. 1949.

Shannon, J. A. Renal tubular excretion. Physiol. Rev. 19: 63–93, 1939.

—— The control of renal excretion of water. I. The effect of variations in the state of hydration on water excretion in dogs with diabetes insipidus. J. Exper. Med. 76: 371–386, 1942.

Smith, H. W. The Physiology of the Kidney. New York, Oxford University Press. 1937.

—— New aspects of renal physiology. J. Urol. 41: 867–876, 1939.

—— Note on the interpretation of clearance methods in the diseased kidney. J. Clin. Invest. 20: 631–635, 1941.

—— Lectures on the Kidney. Porter Lectures Series 9. University of Kansas. 1943.

——, Rangés, H. A., Chasis, H., and Goldring, W. The dispersion of glomerular activity in the normal and hypertensive kidney. (Abst.) Am. J. Physiol. 133: 450, 1941.

Soloff, L. A., and Zatarchini, J. Syndrome of salt depletion. J. A. M. A. 139: 1136–1139, 1949.

Starling, E. H., and Verney, E. B. Secretion of urine as studied on isolated kidney. Proc. Roy. Soc., London, s.b. 97, 321–363, 1925.

Suzuki, T. Zur Morphologie der Nierensekretion. Jena, Gustav Fischer, 1912.

Talbott, J. H., Pecora, L. J., Melville, R. S., and Consolazio, W. V. Renal function in patients with Addison's disease and in patients with adrenal insufficiency secondary to pituitary pan-hypofunction. J. Clin. Invest. 21: 107–119, 1942.

Taylor, F. B., Drury, D. R., and Addis, T. Regulation of renal activity, the relation between the rate of urea excretion and the size of the kidney. Am. J. Physiol. 65: 55–61, 1923.

Terry, R., Hawkins, D. R., Church, E. H., and Whipple, G. H. Proteinuria related to hyperproteinemia in dogs following plasma given parenterally. A renal threshold for plasma proteins. J. Exper. Med. 87: 561–573, 1948.

Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. L., and Prichard, M. M. L., Studies of

the Renal Circulation Springfield, Ill, C. C Thomas, 1947

Van Slyke, D D. Studies in Normal and Pathologic Physiology of the Kidney. Thirtieth Mellon Lecture, May 29, 1947 Ann Arbor, Mich, Edwards Brothers, Inc, 1949

——, Rhoads, C P, Hiller, A, and Alving, A. S: Relation of urea clearance to renal blood flow. Am J. Physiol 110: 387–391, 1934–5

Walker, A M, and Oliver, J. Methods for the collection of fluid from single glomeruli and tubules of the mammalian kidney Am J. Physiol 134: 562–579, 1941.

Warren, J V, Brannon, E S, and Merrill, A. J. Method of obtaining renal venous blood in unanesthetized persons with observations on extraction of oxygen and sodium para-aminohippurate. Science 100: 108–110, 1944.

Wearn, J. T. and Richards, A. N.: Observations on the composition of the glomerular urine with particular reference to the problem of reabsorption in the renal tubules Am. J. Physiol. 71: 209–227, 1924.

White, H L. Observations indicating absence of glomerular intermittence in normal dogs and rabbits. Am J. Physiol. 128: 159–168, 1939.

White, H. L, Heinbecker, P, and Rolf, D: Enhancing effects of growth hormone on renal function Am J Physiol 157: 47–51, 1949.

Wilmer, H A: Renal phosphatase; correlation between functional activity of renal tubule and its phosphatase content. Arch. Path 37: 227–237, 1944.

# 4. Uremia

## Definition

Uremia ("urine in the blood") represents a symptom complex resulting from renal insufficiency due either to an organic or merely functional disorder of the kidney. Within the scope of this definition is included "prerenal" uremia in which renal function is compromised because of an extrarenal disorder of circulation or homeostasis, such as protracted vomiting or diarrhea, diabetic coma, Addison's disease, shock of various types and intestinal obstruction.

## Renal Causes of Uremia

*Any disease of the kidney may result in* uremia if a sufficiently large portion of the organ becomes functionally incapacitated. The amount of intact kidney that is required to keep it functionally solvent depends on the rapidity with which the remainder is destroyed, and on the counterbalance of the opposite kidney. *This is very much the situation that* is found in other organs, such as the adrenal glands, or when there is loss of blood. Obviously a much greater degree of blood destruction may be survived if the loss occurs over a long period of time as against a sudden massive hemorrhage. It is the same with the kidneys. In *chronic renal disease, more than three fourths* of the parenchyma may be destroyed before the renal function is reduced to the uremic level.

More specifically, uremia occurs in acute interstitial nephritis, in acute, subacute, and chronic glomerulonephritis, in eclampsia, and in disseminated lupus erythematosus, occasionally in focal endocarditic glomerulonephritis. It occurs usually in the fatal cases of the necrotizing nephroses, such as those due to mercury bichloride, diethylene glycol, potassium chlorate and chromate, and other agents. Uremia may complicate hemoglobinuric (lower nephron), cholemic, and ethylene glycol nephrosis. Bilateral cortical necrosis, massive infarcts, malignant (accelerated) nephrosclerosis, and polycystic kidneys may be associated with uremia, as may suppurative pyelonephritis, renal amyloidosis, periarteritis nodosa, diabetic glomerulosclerosis, and, of course, *any other diseases associated with excessive* destruction of renal tissue. Only about 7 per cent of the cases of benign arteriolar nephrosclerosis (of essential hypertension) terminate in uremia.

## Clinical Picture of Uremia

*Uremia is a clinical complex of symptoms* that usually, although not always, begins insidiously, generally lagging behind the onset of renal insufficiency. This latent period may vary from several days to a week and in special instances, as in cases of polycystic kidneys, azotemia may be present over a year before symptoms of uremia appear. The uremic signs and symptoms may involve, in addition to the kidneys, (1) the nervous system, (2) the alimentary tract, (3) the respiratory tract, (4) the circulatory system, (5) the skin and (6) miscellaneous organs.

### *The Nervous System*

The nervous signs and symptoms include dull headaches, vertigo, muscular weakness and twitchings, apathy, inability to concentrate, restlessness, neuralgic pains, thick speech, drowsiness or insomnia, transitory or constant disorientation and delirium. *The reflexes may be exaggerated in uremia but abnormal* reflexes do not occur except as a result of complications such as encephalomalacia or hemorrhage. The lowered level of calcium may be responsible for the lively reflexes as well as for the fairly common Chvostek sign. Tetanic manifestations may be initiated also by the *acidosis or by alkalosis due to excessive use of* alkalis, to vomiting, or to overventilation.

### *The Alimentary Tract*

The involvement of *the alimentary tract* manifests itself by dryness of the mouth

the tongue coated brown or grey, uremic ulcerative stomatitis, purpura and loosening of the teeth The stomatitis may cause a particularly offensive, fetid odor of the breath Anorexia, polydypsia, nausea and vomiting may be the initial uremic symptoms and may be mistaken for an intrinsic gastric disorder. Meat may be particularly distasteful. The vomiting, or retching, may be continuous and, at times, projectile, it is thought to be of central origin Fishberg suggests that, in view of the high nonprotein nitrogen content of the gastric juice, the vomiting may serve as a means of vicarious excretion, and, to be sure, one of the current modes of therapy of uremia consists in repeated gastric washings to eliminate the retention products

Constipation may be present at the onset of uremia, but on the other hand, severe diarrhea may be the outstanding symptom of uremia and may be accompanied by tenesmus, cramps and bloody stools The diarrhea, too, may serve to rid the body of waste products The corresponding therapeutic procedure is to wash the gut with dialyzing solution either by means of a two-way tubal system or by surgically isolating a segment of bowel.

### *Respiratory System*

One of the characteristic clinical signs of uremia is the typical uremic odor to the breath The odor is ammoniacal and is believed to be due to the production of ammonia from bacterial decomposition of the abnormally large amount of urea in the saliva Kussmaul breathing, as a result of acidosis, occurs in the late stages The breath sounds are said to be unusually dry and harsh An interstitial pneumonitis occurs frequently in uremia

### *Circulatory System*

Hypertension is commonly associated with uremia but this association is due to the underlying renal disease rather than to the uremia All patients in uremia are not hypertensive The cardiac failure which may occur in uremia is, in most instances, due to coronary insufficiency, or to myocarditis secondary to infection.

Sterile, serofibrinous pericarditis is a common terminal feature of uremia particularly in cases of chronic renal disease. The precise cause of the pericarditis is not known although it is believed to be due to one or more of the retention products. Certainly there is no correlation between the level of any one of the retention products and the development of pericarditis

In recent years, the role of an elevated level of potassium has been given increasing emphasis in the cardiac failure of uremia Hyperkaliemia is common in uremia and may be associated with a characteristic electrocardiographic picture and occasionally with focal myocardial necrosis (plate 28 B). These features are discussed in a subsequent paragraph.

### *Skin*

The skin in uremia is generally dry, waxy, yellowish-brown and pruritic. The yellow color is thought to be due to pigmentation by retained urochromes. The "uremic frost" is not a common phenomenon, when it does occur it signifies impending death The "frost" is due to the deposition of greyish-white urea crystals, mostly on the face, neck and chest (plate 26) Other uremic eruptions include purpuric, erythematous, eczematoid, lichenoid, papular and vesicular rashes Patients in uremia appear also to have an increased susceptibility to drug eruptions.

### *Miscellaneous Manifestations*

The temperature in uremic patients is often subnormal but unusual instances of hyperpyrexia are recorded Emaciation, at times masked by edema, is common in uremia Diphtheritic and hemorrhagic ulcerative colpitis may occur Anemia is the rule and may be of severe degree as well as rapid in development The characteristics are those of a secondary anemia but the mechanism of its production is not clear. In general, however, depression of the bone marrow is favored over hemolysis as the basis for the anemia A hemorrhagic diathesis is common in uremia The coagulation time is usually increased

## Pathogenesis of Uremia

Most of the retention products have been individually held responsible at one time or




FIG. A. *Uremic frost* in a 32 year old patient in *the terminal stage of chronic glomerulonephritis*. The whitish specks of urea crystals are seen especially well near the inner canthus of the eye.

FIG. B. *Uremic frost*. Sections of skin from patient illustrated *in figure A*. *Xanthydrol urea crystals* in epidermis and keratotic follicle. The tissue was treated with xanthydrol.

FIG. C. *Xanthydrol-urea crystals* in a sebaceous gland from patient in figure A.

another for the syndrome and the pathologic changes of uremia. Urea, phosphates, creatinine, guanidine, magnesium, potassium, phenols, aromatic oxyacids and other compounds have been regarded as the basis for the toxicity. In addition, such factors as alterations in osmotic pressure of the blood, dehydration, and salt depletion have been thought to play significant roles In a condition where many kinds of changes occur in the levels of the constituents of the blood, the unitary pathogenetic theories would seem inadequate. It appears more likely that the clinical and pathologic picture may be the resultant of the effect of several of the abnormally accumulated or depleted products rather than of a specific uremic toxin. The problem is not resolved by the experimental administration of the individual retention products and the clinical observation of their effects It is entirely possible that substances that are by themselves innocuous or severely toxic may behave quite differently in their synergistic relationship with other compounds.

### Laboratory Diagnosis of Uremia

*In addition to the signs and symptoms* previously listed, certain laboratory data reinforce the diagnosis of uremia Elevation of blood nonprotein nitrogen and the occurrence of oliguria with low specific gravity of urine is adequate evidence for practical purposes A normal quantity of urine may be excreted when there is extreme renal impairment associated with a maximum specific gravity of 1.010. The mere presence of azotemia is not proof that the symptoms in a given case are due to uremia That is to say, azotemia is of course not synonomous with uremia In such instances of prerenal azotemia, a specific gravity above 1 020 in the absence of oliguria demonstrates as does a normal excretion of phenolsulfonephthalein, that the kidneys are not primarily responsible for the azotemia

In general, a determination of the blood urea nitrogen is preferred to that of nonprotein nitrogen, because urea is a specific individual substance, whereas nonprotein nitrogen represents a variety of substances [urea, creatine, creatinine, uric acid, ammonia, amino acids, and "undetermined nitrogen" (polypeptides, histones)] which may be influenced by extraneous factors. Moreover, inasmuch as urea clearance is a popular investigative procedure in which blood urea nitrogen determinations are also required, there is generally little point to supplementary determinations of the nonprotein nitrogen. However, under certain conditions, knowledge of the blood levels of both urea nitrogen and total nonprotein nitrogen is informative This is particularly true in cases of acute severe hepatic damage in which the failure of the liver to deaminize the amino acids results in low blood concentrations of urea. This decreased level of urea nitrogen, which is noted also in eclampsia, may be deceptive from the point of view of renal function Obversely, the nonprotein nitrogen in cases of acute, widespread, hepatic damage may be abnormally high because of the contribution by the unduly high amino acid fraction. In other words, in the presence of extensive acute hepatitis, the evaluation of renal insufficiency must be made with an awareness that the liver itself is a factor on the one hand, in the elevation of the nonprotein nitrogen and on the other, in the diminution of the level of blood urea nitrogen by failing to release its precursor (amino group) from the amino acids. The ratio of blood urea nitrogen to amino acid nitrogen is normally 2 to 1; in acute necrotizing hepatitis, this ratio is decreased

There is no set level of blood urea nitrogen at which uremic symptoms begin to be noted. Rarely, such symptoms occur when the blood urea nitrogen is less than 100 mg per cent, particularly if the protein content of the diet has been restricted, on the other hand, patients, especially those with polycystic kidneys, may be ambulatory with only minor complaints and with a blood urea nitrogen level over 100 mg. per cent (Fishberg).

The rise in the level of *uric acid* parallels that of urea nitrogen although occasionally extrarenal factors may influence the hyperuricemia In normal pregnancy and in eclampsia, for example, the uric acid in the blood may be disproportionately elevated, and the blood urea nitrogen tends to be low. The elevation of the *creatinine* concentration tends to go



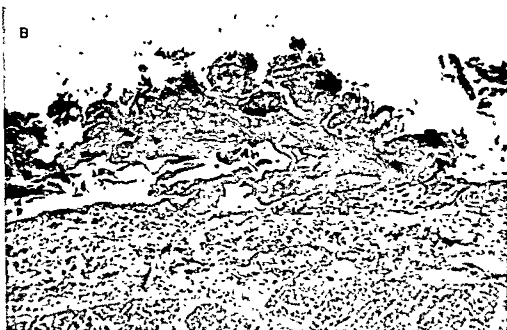




FIG. A. *Sterile uremic fibrinous pericarditis* indistinguishable from a variety of types of pericarditis including rheumatic pericarditis.

FIG. B. *Uremic fibrinous pericarditis* corresponding to the sterile pericarditis illustrated in figure A.

along with the retention of urea. Again, exceptions occur, as in some cases of acute and chronic glomerulonephritis, in which an appreciable rise in the level of urea nitrogen may precede that of creatinine. The relative disparity of glomerular and tubular damage in many cases of glomerulonephritis possibly accounts for this dissociation of the two metabolites.

As a rule, *chloride* is diminished in the blood in renal insufficiency as a result principally of vomiting, decreased intake of salt, and the shift, stimulated by acidosis, of hydrochloric acid from plasma into the red blood cells Moreover, in renal failure, chloride may be excreted into the urine despite a low level of blood chlorides However, in the absence of vomiting, and in some glomerulonephritic patients with edema, the blood chloride level may be elevated, at times to over 1000 mg per cent (as sodium chloride)

*Phosphates*, *sulfates*, and *neutral sulfur* are also increased in renal insufficiency, as are indican and other products of intestinal putrefaction, and often the urochromogens The values for ammonia and magnesium in the blood are not significantly altered, the level of the magnesium may be elevated but slightly (Bradley). Except for those cases with the nephrotic syndrome, or in pregnancy, cholesterol tends to be low in renal failure.

*Potassium in Uremia*

Increasing attention is being paid to the elevated levels of serum potassium in acute renal insufficiency Knowledge of the effects of potassium is one step in the resolution of the problem of the mechanism of uremic intoxication It is now clear that the precipitating cause of death in many cases of uremia is the cardiotoxic effect of hyperkaliemia. Hyperkaliemia occurs also in adrenal insufficiency, severe dehydration and shock

The signs and symptoms of hyperkaliemia (normal 3 5 to 5 3 mEq /liter) are primarily cardiovascular, but may also include listlessness and mental confusion, paresthesias, flaccid pareses or paralyses The cardiovascular manifestations are bradycardia, arrhythmias, poor heart sounds, and peripheral vascular collapse. The electrocardiographic findings, especially when observed serially, may be strongly suggestive of either hyper- or hypokaliemia. With elevated levels of potassium, the first change is in the T-wave which becomes tall and peaked when the serum concentration is from 6 5 to 8 mEq./liter. With higher concentrations, there develop heart block and arrhythmias, wider PR intervals leading to auricular standstill and a biphasic curve with increasing delay in ventricular conduction until cardiac arrest occurs Focal myocardial necrosis has been attributed to hyperkaliemia (plate 28B). Relief of the various signs and symptoms, including reversal of the electrocardiographic changes, follows restoration of the serum potassium to the normal level.

Hypertonic glucose, 10 per cent calcium gluconate, and, above all, restriction of the intake of potassium are of help in combatting potassium intoxication. *It is important to bear in mind that*, whereas the administration of potassium compounds for therapeutic purposes (as in syphilis, bronchitis, etc.) ordinarily does not carry any significant hazard, there is great danger of potassium retention of therapeutically administered potassium salts in the presence of renal insufficiency Moreover, *potassium intoxication may manifest itself at* lower serum levels than would be required in the absence of renal dysfunction Occasionally, deficiency of potassium may exist in the cells (e g , of the myocardium) notwithstanding a normal or even elevated level of serum potassium. This paradoxical situation may be noted in severe dehydration, in which, after fluid has been administered, the serum concentration of potassium may fall to low levels (Darrow)

Infrequently, uremia is associated with hypokaliemia in which the signs and symptoms are muscular pareses, ileus, and electrocardiographic changes consisting of flattened T-waves, depressed ST segments and prolonged A-V intervals In addition, hypokaliemia has been found experimentally to produce tubular necrosis, lipidosis, calcification and dilatation within the kidney (Follis et al.).

*Sodium Depletion*

Data on the mechanism and serious clinical effects of depletion of sodium or sodium chloride

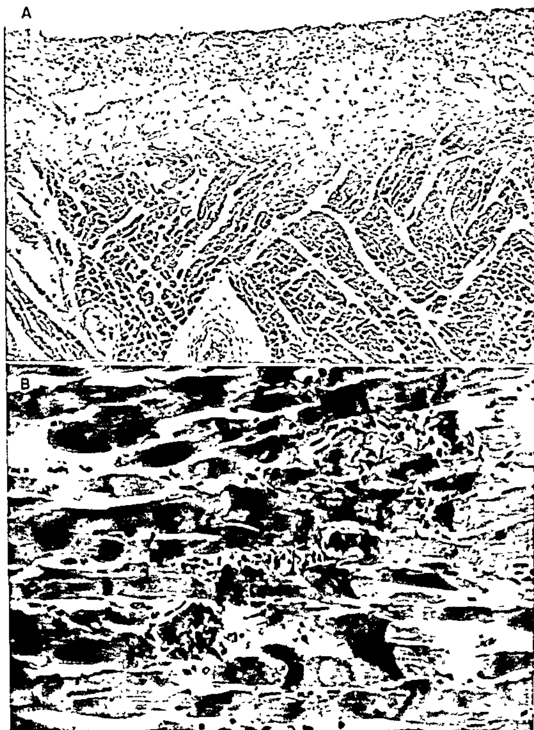



FIG. A. *Uremic pericarditis* without fibrin but characterized principally by lymphocytes and histiocytes.

FIG. B. *Hyperkaliemia* with focal myocardial necrosis, these foci of necrosis were numerous.

furnish still another increment to our information on the mode of toxicity in uremia. In the past, emphasis has been placed on salt restriction in hypertensive and cardiorenal disease because of the potentiating effect of sodium chloride in these conditions Clinically, as well as experimentally (Allen, Selye), however, such restriction of salt, especially in association with loss of salt, may be inadvertently overdone.

It has been observed (Poll and Stern, Soloff and Zatarchni, DeGraff and Nadler) that the excessive loss of salt following salt restriction and mercurial diuresis in patients with cardiac or renal edema may lead to fatal complications. The signs and symptoms of the "salt depletion syndrome" include nausea, anorexia, apathy, mental confusion, muscle cramps, vasomotor collapse, azotemia, and reduction in levels of blood sodium and blood chloride This symptom-complex may be simulated by Addison's disease, sedation, or the natural course of cardiac or renal failure It may be aggravated by the simultaneous loss, in mercurial diuresis, of other electrolytes, such as potassium and calcium

The exact cause of death secondary to disturbed electrolytic homeostasis is not always a simple matter to define In cases of salt depletion, the elevated blood urea nitrogen is contributed to by dehydration (McCance and Robinson), pre-existing renal damage in some cases, and renal impairment as a result of the mercurial diuresis (Binger and Keith). The somnolence, disorientation and stupor are cerebral symptoms and it is suggested that dehydration further compromises the impaired cerebral flow, especially in elderly patients (Jaffe et al.)

### Postmortem Chemical Data

One of the barriers to close physiologic-morphologic correlation is the frequent unavailability of data on the level of blood constituents at the time of or near the time of death. This gap may be corrected in a considerable measure by a study of the body fluids taken during the performance of a necropsy. The data so acquired, however, can not be accepted for direct interpretation at their recorded values because certain enzymatic and other postmortem reactions appreciably alter the antemortem values. Bacterial invasion and autolysis of tissue, abetted by high temperatures, septicemias, and the interval between the time of death and the autopsy, have an appreciable effect on the levels of these constituents and must be evaluated in individual cases.

#### *Glycogen*

It is estimated that 50 to 75 per cent of the glycogen disappears from tissues in the first hour after death (Yater, Osterberg and Hefke). On the other hand, glycolysis occurs in the peripheral blood because of the glycolytic action of bacteria and red blood cells so that artefactitiously lowered values may be expected It is reported that increased levels of glucose have been found in the left chamber of the heart as a result of glycogenolysis of the myocardial glycogen (Naumann). It is also of interest that the postmortem level of glucose is raised in the hepatic vein and, by diffusion, in the inferior vena cava and right heart, by the process of glycogenolysis that takes place in the liver.

#### *Urea, Creatinine, Uric Acid*

In the case of urea, creatinine and uric acid, the postmortem values tend to be higher—at times markedly higher—than the antemortem levels The elevation is attributed to the prerenal azotemia resulting from terminal or agonal circulatory failure, disintegration of tissue and sepsis (Naumann, Hamilton). In one instance of a 27 year old woman with intestinal obstruction and peritonitis, the levels of non-protein nitrogen and of creatinine were 29 2 mg per cent and 1 27 mg per cent respectively one day before death, at autopsy done within 24 hours after death, the level of the blood creatinine was 7 26 mg. per cent (Hamilton)

Of the three substances, the postmortem value for creatinine most closely approximates the level before death It is about twice the antemortem level but it represents a more reliable determination than that of urea or uric acid The level of urea ten hours after death is about three to six times the antemortem value. The postmortem value of uric acid ten hours




Fig. A. *Uremic colitis* with shaggy diphtheritic mucosal inflammation and ulceration with blood clots.

Fig. B. *Uremic ulcer* (arrow) in duodenum which resulted in severe hemorrhage.

after death is also about twice its antemortem level Cerebrospinal fluid appears somewhat more dependable than blood for these determinations, particularly for glucose (Naumann) but it is, of course, not as easily secured The determinations of the chloride content of blood are generally agreed to be unreliable (Hamilton) Postmortem urinalysis may furnish confirmatory data.

## Pathology of Uremia

### *Kidneys*

As already indicated, in uremia the kidneys may show the picture of any disease which compromises a sufficient amount of parenchyma These include the various forms of glomerulonephritis, necrotizing nephroses, acute interstitial nephritis, bilateral cortical necrosis, polycystic disease, amyloidosis, myeloma nephrosis and the different vascular diseases. Or, as in the cases of prerenal uremia, the kidneys may show no significant alterations

### *Skin*

The skin may have a variety of lesions none of which is specific for uremia except the uremic frost. Urea crystals responsible for the "frost" are demonstrable by the xanthydrol reaction The crystals are arranged in yellowish green fine sheaves, are birefringent, and are distributed within the cutis, epidermis and appendages (plate 26). Similar crystals may be found in practically every organ from cases in which there has been a pronounced elevation of blood urea nitrogen Other histologic reactions occasionally seen are those of pemphigus, eczema, toxic erythema and purpura.

### *Lungs*

The lungs in uremia often present a histologic picture of mild interstitial pneumonitis which is most marked at the hila Radiologists have come to recognize that the sunburst shadows radiating from the hila of the lungs may represent the interstitial pneumonitis of uremia (plate 31 A) The differential radiologic diagnosis in these cases includes, above all, simple hilar congestion Histologically, the picture resembles that of other varieties of interstitial pneumonitis and is characterized by mononuclear cell infiltration of the alveolar septa, edema, histiocytes within alveolar fluid and fibrinous bands at the periphery of the alveoli (Urea crystals may be demonstrated (plate 31 B) by placing the tissue in 5 per cent solution of xanthydrol in glacial acetic acid for 5 to 6 hours. The tissue is then washed in running water for 30 minutes, fixed in formalin, dehydrated thereafter in the usual manner, and cut as ordinary paraffin sections )

### *Heart*

Sterile serofibrinous pericarditis of some degree is present in about a third of the cases of uremia (plate 27). Occasionally, the pericarditis is as striking as in a case of severe rheumatic pericarditis and is of the "bread and butter" variety There is no relationship between the pericarditis and any underlying myocarditis Focal nonspecific myocarditis of mild extent has been attributed to uremia. Calcification of myocardial fibers has been recorded in uremia (Scholz; Brown and Evans; Gore and Arons) The incidence of myocardial calcification in uremia is low, but when extensive, is almost always in association with uremia. Occasionally, scattered, minute foci of myocardial necrosis are found in association with hyperkaliemia (plate 28 B).

### *Spleen*

For pathogenetic reasons that are not obvious, the spleen may be diffusely speckled with greyish white foci of necrosis, three to four millimeters in diameter. Such spleens are referred to as "fleckmilz" or speckled spleen or Feitis spleen No thrombi or other organic vascular alterations account for the necrosis (plate 31 C).

### *Pancreas*

In the pancreas, dilatation of acini by inspissated secretion is seen in a mild to marked degree in about 39 to 52 per cent of cases of uremia (Baggenstoss) (plate 30 C). In only about 6 to 15 per cent of cases, however, is the lesion diffuse This same lesion occurs in instances of severe protracted diarrhea or vomiting and is not at all specific for uremia.

### *Gastro-intestinal Tract*

Ulcers may occur anywhere along the alimentary tract from the mouth to the anus.

# PLATE 30. UREMIA




FIG A *Focal hemorrhagic ileitis* in uremia

FIG B *Uremic ulcer* of duodenum with underlying partially necrotic, thrombosed arteries

FIG C *Uremic ulcer of colon*

FIG D *Pancreas in uremia* with dilated acini filled with inspissated secretion, a picture occurring occasionally in uremia, but also commonly with severe diarrhea, vomiting and dehydration.

The involvement may appear as discrete ulcers or as a diffuse segmental enteritis that may be grossly or histologically indistinguishable from the colitis due to bacillary dysentery, aplastic anemia or mercury colitis (plates 29, 30) Jaffé and Laing believed the ulceration to be secondary to hemorrhages into the mucosa The ulceration may be responsible for massive fatal intestinal hemorrhages following secondary necrosis of underlying arteries Uremia in association with hypertension may produce necrotizing arteriolitis and arteritis of bowel with subsequent ulceration and hemorrhage. The hemorrhagic diathesis of uremia may also involve the vagina with the production of hemorrhagic ulcerative colpitis

*Brain*

Edema of the brain and meninges with focal encephalitis may occur in uremia.

TREATMENT OF UREMIA

Inasmuch as the precise chemical agent or agents responsible for the signs and symptoms of uremia are not known, the aim of the therapy has naturally been to restore the fluid equilibrium and the chemical composition of the blood to normal levels This objective is accomplished by a keenly calculated addition of fluids, electrolytes, and other essential agents, abetted by vicarious excretion Chemical imbalance is pretty much the same whatever the cause of the renal failure, so that the therapeutic objective remains essentially constant The imbalances are the loss of water, the fall in blood calcium, the increase of phosphate and potassium, as well as of acid metabolites which lower the carbon dioxide combining power and the pH of the blood, and, of course, the azotemia. Conservative attempts should be made to correct these imbalances Too often overcorrection, particularly of fluid and alkali restoration, is achieved with disastrous results.

The more active methods that currently have caught the fancy of workers in the field of acute renal failure are exsanguination transfusions or variants of procedures of dialysis in which an irrigating fluid of special composition is applied to peritoneal or intestinal surfaces in order to extract the retention products by the principle of osmosis. The methods include (1) intubation and irrigation of the stomach, (2) isolation of a segment of bowel with irrigation by the dialyzing fluid, (3) peritoneal irrigation, and (4) the "artificial kidney" of Kolff which conveys the patient's arterial blood to a dialyzing apparatus and then returns the blood to the patient's vein The composition of the dialyzing fluid is of this order:

| | Gm/liter |
|---|---|
| NaCl | 7.25 |
| KCl | 0.2 |
| $CaCl_2$ | 0.1 |
| $MgCl_2 \cdot 6H_2O$ | 0.2 |
| $NaHCO_3$ | 1.5 |
| Glucose | 10.0 |
| Gelatin | 10.0 |
| (pH 7.4) | |

The great difficulty in evaluation of the therapy of acute renal failure is that a high percentage of cases recovers spontaneously, usually between the seventh to fourteenth day of uremia Because of this fact, the nicest judgment is required for the decision as to when to replace or supplement conservative therapy with a dialyzing procedure. The skill required to carry through the dialyzing procedures without complications such as peritonitis, hemolysis, clotting, pyrogenic reactions, leaks, edema, and inadequate flow control make the decision all the more difficult. A useful and favorable survey of the subject may be found in the papers of Merill and his associates.

Other therapeutic procedures in the treatment of acute renal failure include renal decapsulation and sympathetic block. The renal decapsulation has been performed on the assumption that the kidney in acute renal failure (e g, mercury bichloride or hemoglobinuric nephrosis) is swollen and encased in a constricting capsule However, the beneficial results that have been reported are more on the basis of spontaneous recovery or perhaps the resection of renal sympathetic nerves incidental to the decapsulation rather than to the relief of the effects of interstitial edema. The interference with the nerve supply has been effected with variable results by means of intravenous administration of procaine, spinal anesthesia and the block of lumbar sympathetics. Occasionally




FIG A *Interstitial pneumonitis* of the type that may occur in uremia as well as in other conditions such as virus or rickettsial pneumonia and rheumatic fever.

FIG B *Xanthydrol urea crystals (xanthydrol reaction)* in lung of patient with uremia and "uremic pneumonitis"

FIG C. "*Fleckmilz*" or spotted spleen of Feitis with focal necrosis in uremia

the results are striking as in the case in which the lumbar sympathetics were infiltrated with procaine with initiation of diuresis The diuresis of 24 hours duration was followed by anuria again, so that the infiltration of procaine was repeated and diuresis promptly recurred

The block of renal sympathetic supply is based on the theoretically sound rationale that experimental stimulation of the renal sympathetic nerves produces glomerular ischemia and resection of them results in glomerular hyperemia. The lack of adequate glomerular filtration seems by all odds the most likely immediate explanation of the oliguria or anuria in the cases of acute renal failure as opposed to the concept of complete reabsorption of adequate glomerular filtrate through necrotic tubules into the peritubular capillaries This matter will be considered further in the discussion of the nephroses.

### Prerenal Azotemia

Prerenal azotemia refers to the situation in which the retention products of true uremia occur for reasons not accounted for by the histologic changes in the kidneys Nevertheless, despite the absence of significant morphologic renal alterations, there is renal insufficiency which may be of a marked degree The conditions leading to prerenal azotemia include severe and protracted vomiting as in intestinal obstruction or eclampsia, profuse loss of intestinal contents through a fistula or by diarrhea, severe intestinal hemorrhage, some liver diseases, diabetic acidosis, various types of shock, the crises of Addison's disease, cardiac failure and dehydration.

The presence of blood in the intestinal tract, as from a bleeding peptic ulcer, often is followed by azotemia, and deserves additional comment The increase in the level of the nonprotein nitrogen after a single massive hemorrhage begins to take place in about six hours and reaches its maximum within 24 hours, but occasionally within 48 hours (Schiff and Stevens). Levels above 100 mg per cent of blood urea nitrogen have been recorded after hemorrhage into the intestinal tract (Schiff and Stevens). The elevated values for blood urea nitrogen are attributed not only to resorption of the nonprotein nitrogenous products from the blood within the intestinal tract, but to the additional factors of shock, dehydration, malnutrition, and renal insufficiency which may accompany the loss of blood

#### *Signs and Symptoms*

Notwithstanding the usual lack of conspicuous renal morphologic changes, prerenal azotemia may be accompanied by the clinical picture of uremia, such as lassitude, muscular twitching, vomiting, diarrhea, urinous breath, and coma. However, in contrast to uremia from organic renal insufficiency, pericarditis rarely accompanies prerenal azotemia

Just as in uremia due to organic renal disease, in prerenal uremia, a rise occurs in the levels of uric acid, creatinine, and urea nitrogen, sometimes to enormous values of over 400 mg. per cent (NPN) Hypochloremia is common Acidosis may occur in association with diabetic coma or Addison's disease, and alkalosis may result from vomiting. Oliguria and even anuria may be present although occasionally there is polyuria The specific gravity tends to become progressively lowered. Moderate albuminuria along with some hyaline and granular casts, and a few red and white blood cells may be present in the sediment. Tests for renal function, such as urea clearance, and concentration tests, reveal abnormal function in most cases. The physiologic alterations most often responsible for the functional disturbance of the kidney in prerenal azotemia are the reduced renal blood flow, and the electrolytic imbalance of sodium and potassium particularly

With regard to renal azotemia associated with congestive cardiac failure, it is worth noting the contributory role of the renal tubules to the aggravation of the edema due to cardiac failure As part and parcel of the cardiac failure, there is reduced renal blood flow to about one third or one fifth of normal, while the glomerular filtration is reduced to from two thirds to one half With the reduction of glomerular filtrate, there is not a parallel reduction in salt reabsorption, on the contrary, it is as if the tubules, receiving a diminished supply of glomerular filtrate, "pull" harder to reabsorb a disproportionate amount of salt in an at-

tempt to equal the amount of salt they reabsorb normally. The increased salt retention is a central factor leading to increased plasma volume, distention of veins and edema.

Unlike the grave prognosis of uremia caused by organic renal disease, prerenal azotemia may be quickly resolved if the primary physiologic disturbance leading to the azotemia is cleared. This restoration is often not achieved because the basic physiologic disorder of electrolytic or fluid imbalance, or reduced renal blood flow, is recognized too late or not at all

REFERENCES


ALLEN, F M Arterial hypertension J A M A 74: 652–655, 1920

ALSTED, G Further studies on azotemia following hemorrhage in the digestive tract Am J M Sc 192: 199–209, 1936

BAGGENSTOSS, A H The pancreas in uremia, a histopathologic study Am J Path 24: 1003–1017, 1948

BECHER, E Chromogens in serum and urine in kidney diseases, light color of urine in contracted kidney Deutsches Arch f klin Med 148: 40–57, 1925

—— Pathogenesis of uremia Zentralbl f inn Med 46: 369–383, 1925

BINGER, M W., AND KEITH, N M The effect of diuretics in different types of edema J A M A 101: 2009–2016, 1933

BRADLEY, S E Biochemical abnormalities during renal insufficiency New England J Med 235: 791–798, 1946

—— The Pathologic Physiology of Uremia in Bright's Disease Springfield Ill C C Thomas, 1949

BRIGHT, R Cases and observations illustrative of renal disease accompanied with secretion of albuminous urine Guy's Hosp Rep 1: 338–400, 1836

BROWN, C F, AND EVANS, W D Primary, massive calcification of myocardium Am Heart J 19: 106–113, 1940

DARROW, D C Body fluid physiology the role of potassium in clinical disturbances of body water and electrolyte New England J Med 242: 1014–1018, 1950

DEGRAFF, A C, AND NADLER, J E Review of toxic manifestations of mercurial diuretics in man J A M A 119: 1006–1011, 1942

FEITIS, H Ueber multiple Nekrosen in der Milz (Fleckmilz) Beitr z path Anat u z allg Path 68 297–332, 1921

FISHBERG, A M Hypertension and Nephritis, 4th Ed Philadelphia, Lea and Febiger, 1939

FOLLIS, R H, JR, ORENT-KEILS, E, AND MCCOLLUM, E V The production of cardiac and renal lesions in rats by diets extremely deficient in potassium Am J Path 18: 29–39, 1942

GORE, I, AND ARONS, W Calcification of the myocardium Arch Path 48: 1–12, 1949

HAMILTON, R C Postmortem blood chemical determinations, a comparison of chemical analyses of blood obtained postmortem with degrees of renal damage found at autopsy. Arch. Path 26: 1135–1143, 1938

HARRISON, T R, AND MASON, M. F The pathogenesis of the uremic syndrome Medicine 16: 1–44, 1937

JAFFE, H L, MASTER, H L, AND DORRANCE, W The salt depletion syndrome following mercurial diuresis in elderly persons Am J M Sc 220: 60–65, 1950

JAFFÉ, R H, AND LAING, D Changes of digestive tract in uremia, pathologic anatomic study Arch Int Med 53: 851–864, 1934

KEITH, N M, BURCHELL, H B, AND BAGGENSTOSS, A H Electrocardiographic changes in uremia associated with high concentrations of serum potassium Am Heart J 27 817–844, 1944

——, KING, H L, AND OSTERBERG, A E Serum concentrations and renal clearance of potassium in severe renal insufficiency in man Arch Int. Med 71: 675–701, 1943

KOLFF, W J The artificial kidney J Mt Sinai Hosp 14. 71–79, 1947

LEITER, L Observations on the relation of urea to uremia Arch Int Med 28 331–354, 1921

—— The role and control of renal dysfunction in congestive heart failure New York State J Med 48: 1803–1806, 1948

MCCANCE, R A, AND ROBINSON, J R Evaluation of renal clearances Proc Roy Soc Med 42: 475–480, 1949

MERRILL, J P, THORN, G W, CALLAHAN, E J, III, AND SMITH, L H, JR The use of an artificial kidney I Technique J Clin Invest 29: 412–424, 1950

——, SMITH, S III, CALLAHAN, E J, III AND THORN, G W The use of an artificial kidney II Clinical experience J Clin Invest 29: 425–438, 1950

NAUMANN, H N Studies on postmortem chemistry Am J Clin Path 20: 314–325, 1950

POLL, D, AND STERN J E Untoward effects of diuresis with special reference to mercurial diuretics. Arch Int Med 55: 1087–1094, 1936

RABINOWITCH, I M Relative proportions of sodium, potassium, calcium and magnesium in blood plasma in renal disease J Biol Chem 62: 667–673, 1924–5

RABY, G Multiple infarcts and necroses of the spleen (Fleckmilz) Am J Path 8 107–115, 1932

SCHIFF, L T, AND STEVENS, R J Elevation of

urea nitrogen following hematemesis or melena. Arch Int. Med 64: 1239-1251, 1939.

SCHOLZ, T. Calcification of heart; its roentgenologic demonstration, review of literature and theories on myocardial calcification. Arch Int Med 34: 32-59, 1924

SELYE, H. Textbook of Endocrinology. 2nd Ed Montreal, Acta Endocrinologica, 1949.

SOLOFF, L A, AND ZATARCHNI, J Syndrome of salt depletion J. A M A. 139: 1136-1139, 1949

STEWART, H J, SHEPARD, E M., AND HORGER, E. L Electrocardiographic manifestations of potassium intoxication Am. J. Med 5: 821-27, 1948.

TARAIL, R, AND ELKINTON, J. R.: Potassium deficiency and the role of the kidney in its production. J. Clin. Invest. 28: 99-113, 1949

VERMOOTEN, V., AND HARE, D. M. The use of continuous gastric lavage in the treatment of uremia with potassium J. Urol. 59: 907-919, 1948.

YATER, W M., OSTERBERG, A E., AND HEFKE, H. W Clinical determination of glycogen ratio of heart muscle and bundle of Hiss in man. Proc Staff Meet, Mayo Clinic 3: 243, 1928.

# 5. Malformations

The maldevelopments of the kidney, as would be expected, are concerned with (1) number, (2) size, (3) position, and (4) disorganization of architecture (plates 32, 33)

It appears generally to be true that anomalous kidneys are predisposed to inflammations of various sorts, including glomerulonephritis and pyelonephritis It seems likely that the basis for this predisposition is the interference with urinary excretion often inherent in malplaced or rotated kidneys, especially in conjunction with anomalies elsewhere in the urinary tract

Malformations may be classified as follows.

- Agenesia
- Hypoplasia
- Supernumerary kidney
- Ectopia
- Anomalies of fusion
- Vascular anomalies
- Anomalies of renal pelvis
- Cysts
  - Solitary
  - Polycystic

### 1 Bilateral Renal Agenesia

Up to 1910, the reported cases of bilateral renal agenesia totaled 135 (Hinman) Of 2100 stillbirths, agenesia occurred in 7, or 1 in 343 (Bell) Potter noted 20 cases of renal agenesia (17 in males) in 5000 autopsies on fetuses and newborn infants Infants with this deficiency are almost always stillborn, although Rosenbaum reported the case of an infant that survived 11 days The condition occurs predominantly in males (a ratio of about 2½ to 1) for obscure reasons, and is associated with oligohydramnios in most cases Usually the ureters are also absent but portions of them are occasionally present The bladder was absent in three of Bell's cases and was abnormally small in two others All of Bell's cases were premature infants It is worth noting that fetuses may survive to term, and even somewhat longer without any kidneys Some other developmental anomaly, especially of the genital organs, is often present. In all of Potter's cases there was hypoplasia of the lungs, and in all three females, the uterus and vagina were absent, although the fallopian tubes were present She also observed characteristic facies in these infants with features that included (1) flattened tip of nose, (2) elongated lobes of ears, (3) receding chin, (4) prominent fold about inner canthus of the eyes, and (5) increased space between the eyes The facies are striking, but may be observed in infants with other renal anomalies, as with polycystic kidneys (plates 32 A, 36 A) There is no relationship between the occurrence of renal agenesia and maternal age, parity, or complications of pregnancies

### 2 Unilateral Renal Agenesia

In Bell's series of 35,329 autopsies, complete absence of one kidney occurred in 68 cases, or in 1 out of 519 cases, there was about one-half this frequency in Eisendrath's group Single *pelvic* kidneys occur approximately once in 22,000 persons (Stevens) Of 2100 stillbirths, there were 16 cases of unilateral renal agenesia, or 1 in 150 (Bell) As would be expected, the greater number of cases is found among stillbirths, not because a solitary kidney is incompatible with life, but because anomalies are usually multiple, and renal agenesia is likely to be associated with other compromising anomalies For example, of Bell's 68 cases, 16 occurred in stillbirths, 6 more were found in infants less than 1 week old. However, after this initial period was survived, the age incidence was fairly evenly distributed through all decades

Unlike the sex incidence of bilateral renal agenesia, there is no significant difference in the frequency of solitary kidney in males and females below one year of age, although the predominant incidence in males (about 2 to 1) is manifest after that period (Bell) Agenesia, again for reasons unexplained, is somewhat more likely to occur on the left side than on the right, for example, in Collin's large series, the left kidney was absent in 51 7 per cent and the right in 40 9 per cent. (4 4 per cent not stated)

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The absence of the kidney may be associated with various conditions of the corresponding ureter, and ureteral orifices The ureter is completely absent in most cases. In some, there is evidence of a vestigial ureteral structure, varying from a dimple in the bladder to a structure extending for a length of several centimeters, and rarely for the entire distance of a normal ureter In most cases, the ureter is reduced to a fibrous cord Occasionally it ends ectopically in the seminal vesicle. The renal artery and vein do not develop The ipsolateral adrenal gland is stated to be present in 75 per cent of cases (Eisendrath), in many instances there is no mention of the adrenal gland in the autopsy protocol

Associated anomalies of other organs are present in the majority of cases. In adults, according to Fortune, about two thirds of the females had malformations of the genital tract, such as bicornuate uterus or atretic vagina. In the male there is often absence or anomalies of the epididymis, ductus deferens, seminal vesicles and ejaculatory duct on the side of agenesia of the kidney Bell found very few anomalies associated with solitary kidney in adults; the infants were most affected and exhibited spina bifida, meningocele, imperforate anus and other maldevelopments.

### Morphogenesis of Renal Agenesia

The morphologic basis of renal agenesia would seem theoretically to result either from a lack of metanephrogenic primordium from the nephrogenic cord, a failure of the ureteral bud to develop from the wolffian duct, or a lack of proper contact ("organizer" influence) between the ureteral bud and the nephrogenic cord Presumptive clues derived from associated anomalies, such as frequent absence of ureter and ductus deferens point to the wolffian duct as the source of the dysembryogenesis. As Boyden indicates, there is likelihood that the wolffian duct does not reach the cloaca and, to be sure, renal agenesia may be produced experimentally in embryos by interrupting the wolffian duct This same mechanism may account for unilateral as well as bilateral renal agenesia Often, renal hypoplasia is mistaken for agenesia, an error that may be avoided by sectioning the remnants of tissue in the renal fossae, and discovering vestiges of atrophic or poorly developed nephrons

### Status of the Solitary Kidney

The solitary kidney is usually considerably larger, and often twice the weight of a normal kidney. The enlargement is teleologically attributed to a compensatory hypertrophy and is so frequent in solitary kidneys that encountering a large otherwise normal appearing kidney should recall the possibility of the absence or hypoplasia of the opposite organ. The solitary kidney is usually in the normal position, but is occasionally found in the iliac fossa and the true pelvis, and in some instances is abnormally rotated

The general tendency of the *predisposition* to inflammation of anomalous kidneys applies to the solitary kidney too. In this case, the predisposition may be enhanced by associated anomalies of renal vessels or of the ureter, leading to interference with drainage of urine. Of Bell's 68 cases of congenital solitary kidney, there were four with hydronephrosis, and four with duplication of the ureter. In the absence of any untoward inflammation, the solitary kidney is able to maintain renal sufficiency inasmuch as the "factor of functional safety" of the kidneys is about 5 to 1. However, Nation found that in 6 out of 27 cases of unilateral renal agenesia,

Fig A *Facies characteristic* of infants with renal agenesis including prominent canthal fold, large low set ears, receding chin and flattened nose

Fig. B *Bilateral renal agenesia*. Black dots beneath adrenals indicate vestigial kidneys.

Fig C *Unilateral renal agenesia*, occasionally associated with one or two rudimentary ureters

Fig D. *Unilateral renal hypoplasia*

Fig E *Ectopic kidney* over aorta Ureter in midline

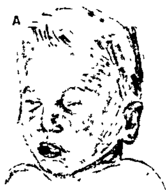
Fig F. *Unilateral renal pelvic ectopia*

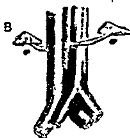
Fig G *Bilateral renal pelvic ectopia*

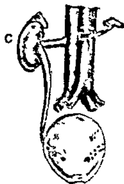
Fig H. *L-shaped kidney* (fused)

Fig. I. *Sigma shaped kidney* (*fused*).

## PLATE 32. Congenital Anomalies



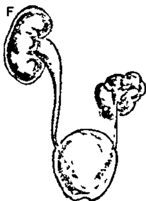



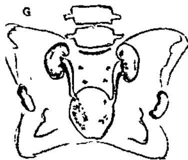



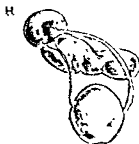










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death was caused by renal insufficiency, produced in 3 of these by "congenital inadequacy."

## Unilateral Renal Hypoplasia

Unilateral renal hypoplasia occurred 77 times in 63,076 autopsies, or 1 in 816 (Eisendrath). The unequivocal determination of the pathogenesis of a single dwarfed kidney is often impossible to achieve The reason for this difficulty is that the end stages of renal inflammation occurring early in life may be indistinguishable from congenitally hypoplastic kidneys The decision as to what the upper weight limit of a hypoplastic kidney should be is an arbitrary one and has been set at 60 grams by Bell Within this weight limit will be included not only congenitally hypoplastic kidneys but also instances of unilateral chronic pyelonephritis and kidneys whose blood supply has been compromised by trauma or disease In addition, of course, some kidneys with chronic pyelonephritis, chronic glomerulonephritis, and benign nephrosclerosis may undergo so marked a degree of bilateral contraction that they fall within the weight range of hypoplasia The gross and histologic criteria for the diagnosis of glomerulonephritis, pyelonephritis and nephrosclerosis are described elsewhere However, it is apparent that these three conditions, particularly the first two, may be superimposed on a congenitally hypoplastic kidney and so obscure the diagnosis

True congenital hypoplasia of the kidney may take one of the following forms:

1 Miniature replicas of adult kidneys, with, however, fewer reniculi or lobes, for example, 3 to 5 rather than a normal number of about 12 to 18 (plate 72A) The number of calyces is correspondingly reduced The glomeruli tend to be large and the tubules dilated Correspondingly, urography would reveal a triangular or ampullary pelvis leading into minor calyces without intermediate major calyces, or the pelvis would be small and show only one or two calyces It has been suggested that [illegible]

nephrogenic mass is another possibility

2. Single or multiple cysts, dilated tubules and more or less intervening fatty, fibrous or calcified interstitium often with sclerotic arteries (plates 40, 41).

Additional features to consider are the size of the renal pelvis and the renal arteries. If the renal pelvis is disproportionately large in comparison with the parenchyma, atrophy due to hydronephrosis obviously must be suspected. Similarly, if the appertaining renal artery was originally (prior to endarteritis of disuse) of a caliber larger than that anticipated for the size of the organ supplied, the presumption is that the kidney became atrophic for reasons other then dysembryogenesis.

The functional capacity of the congenitally hypoplastic kidney naturally varies with the amount of residual parenchyma, but, at best, the small organ, by itself, may be assumed to be incapable of sustaining life. In some instances, the unilateral hypoplastic kidney with a normal opposite kidney has been associated with and perhaps responsible for hypertension (Higbee) Nation differentiates the hypoplastic from the aplastic kidney on the basis of evidence of the total lack of function of the latter from its beginning

## Bilateral Renal Hypoplasia

There are numerous reports of marked hypoplasia of both kidneys, which, as in bilateral agenesia, is associated, as a rule, with stillbirth Cases of lesser severity survive several months or a few years until death occurs in uremia, often accompanied by rickets and by poor or dwarfed development of the child As indicated,

Fig. A *Horseshoe* kidney (fused)

Fig B *Caked kidney* (fused)

Fig. C *Crossed ectopia* with fusion.

Fig D. *Crossed ectopia* without fusion.

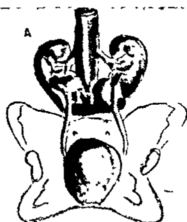
Fig E *Ectopia of hypoplastic kidney* in bladder wall with contralateral hydronephrosis

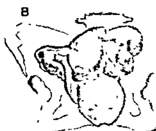
Fig F. *Faulty rotation* of right kidney.

Fig G *Anomalous renal vessels* with constriction and hydronephrosis

Fig H *Extra-renal pelvis.*

Fig. I. *Polycystic kidney*



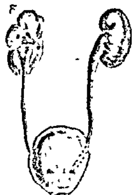


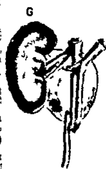

















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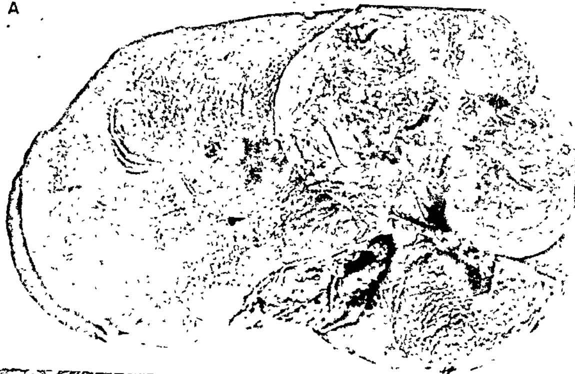









FIG. A *Solitary cyst of kidney* The evidence suggests that these are acquired rather than congenital

FIG. B *Partially calcified wall* of large cyst of kidney which could be visualized radiographically

FIG. C. *Small solitary intraparenchymal cyst* with partially calcified contents



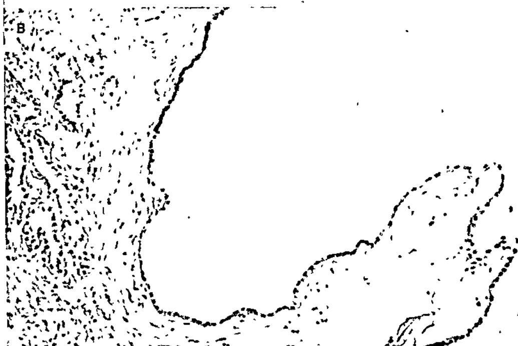




FIG A *Solitary cyst of kidney*

FIG B *Solitary cyst showing* epithelial lining resembling that of a distal convoluted tubule

when the so-called congenital bilateral hypoplasia of kidneys of adults are carefully screened, it is found that very few are left after the small contracted kidneys of chronic glomerulonephritis, chronic pyelonephritis and benign nephrosclerosis are removed

### Supernumerary Kidney

One of the rarest of renal anomalies is the supernumerary kidney Until 1944, 46 such instances had been reported (Exley and Hotchkiss) The term "supernumerary kidney" should be reserved for a third kidney which is entirely free from its adjacent kidney or only loosely attached It may lie above the normal kidney, but usually lies inferiorly and occasionally in the pelvis. This definition distinguishes the supernumerary kidney from the fused kidney or double kidney The blood supply is variable and tends to be derived from the closest arterial source, such as the aorta, or normal renal artery In the majority of cases, the ureters of the supernumerary and ipsolateral kidney fuse somewhere along their course, commonly just proximal to their entrance into the bladder. However, the ureters may be reduplicated so that three ureteral orifices may be present Occasionally the third ureter ends in the vulva, vagina, or prostatic urethra.

The supernumerary kidney is smaller than normal unless enlarged by hydronephrosis, cyst or neoplasm The first authentic case of adenocarcinoma in such a kidney is stated to be that of Exley and Hotchkiss

#### *Embryogenesis of Supernumerary Kidney*

The supernumerary kidney arises presumably because of the development of a second ureteral bud from the mesonephric duct, which then is able to make contact with a portion of the primordial nephrogenic mesenchymal tissue If the two ureteral buds arise in close enough proximity to each other, they may then invade their single overlying metanephrogenic cap to form fused or double kidneys

### Ectopia of Kidneys

Congenitally displaced kidneys in most instances lie in the iliac fossa, on the brim of the pelvis, or in the pelvic cavity, a few are displaced to the midline or to the opposite Renal ectopia occurs in a ratio of approxim 1 to 750 autopsies without selective se cidence. There is a greater incidence of di tions of size and shape in those ectopic kid that are in the pelvic cavity than in thos cated more superiorly in the iliac fossa Pos the pressure of adjacent organs on displ kidneys lacking the normal fatty cushion factor in their altered shape. The renal p is usually directed ventrally although some dorsally. Often the ectopic kidney is cong tally hypoplastic; occasionally both kidneys displaced and fused. A congenitally soli kidney may also be displaced in the pelvis ureter tends to be short and because of its p tion, vulnerable to obstruction. The arterie the ectopic kidney in most instances arise f the adjacent portion of the aorta or iliac teries and rarely from the normal level in aorta. The veins drain into nearby ves (Harris).

The ectopic kidney is subject to the m ordinary complications of the normal kid However, by virtue of its disadvantageous p tion, from the point of view of pressure by ad cent organs on the ureter, hydronephrosis, onephrosis, pyelonephritis and nephrolithi are particular hazards. In the presence of a of these complications, it is obvious that clinical picture may simulate gynecologic orders, or bowel involvement, such as pendicitis In some instances, a pelvic kid has been responsible for serious dystocia T diagnosis of ectopic kidney has been made the observation of abnormally located shado of calculi in the flat-plate, with urography, a by palpation of a mass behind the ute (Coppridge)

### Crossed Ectopic Kidney

The crossed ectopic kidney is distinguish from the double kidney and the fused horsesh kidney (i e , the kidney of median fusion). the case of crossed ectopia, the renal blaster becomes deviated to the opposite side where usually lies caudal to the normal or "fixe kidney The ectopic kidney may develop sep rately or may become completely fused wi obliteration of the lines of demarcation. T

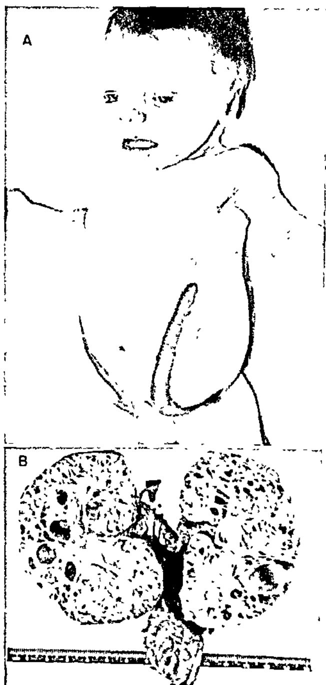
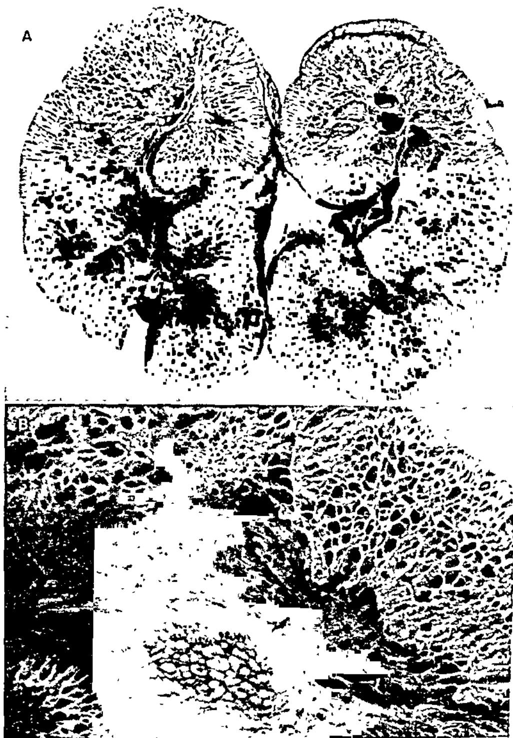



FIG A *Two week old infant* with bilateral polycystic kidneys indicated by abdominal markings and illustrated in figure B This infant has the facies described in cases of renal agenesis the prominent fold about the inner canthus, the receding chin, the flattened tip of the nose, and the enlarged ears

FIG B *Polycystic kidneys* from infant in figure A




FIGS A AND B *Infantile polycystic kidney* in two magnifications showing the diffusely and regularly honeycombed appearance which is the usual appearance of the polycystic kidney of infants, as opposed to adults Too much parenchyma is destroyed to permit survival to adult life (Courtesy of W. A D. Anderson From *Pathology*, St Louis, C V Mosby, 1948)




FIG. A. *Honeycombing of infantile congenitally polycystic kidney* from type illustrated in figures A and B, plate 37

FIG. B. *Higher magnification* of polycystic kidney illustrated in figure A.

FIG. C. *Congenitally polycystic liver* associated with polycystic kidney of figure B. Cysts appear to arise from bile ducts

hilum may face in any of a variety of directions depending on the degree of rotation of the kidneys The so-called "fixed" kidney may also show an abnormal position of its hilum. The ureters do not unite but terminate in separate ostia, generally in the normal position in the bladder. Inasmuch as it is the caudal kidney that is usually the ectopic one, its ureter crosses the midline to end in the ureteral orifice of the opposite side. In its passage to the bladder, the ureter may take an abnormal route, sometimes coursing behind the rectum

As with many other anomalies of the kidneys, there is no diagnostic symptomatology associated with crossed ectopia However, the importance of ascertaining the existence of a fused ectopic kidney when nephrectomy is under consideration is obvious In the great majority of instances, the length of the fused ectopic kidney, which is greater than normal, offers by itself some clue as to diagnosis The presence of a line of demarcation between the two fused kidneys is additional presumptive evidence, but considered alone this does not differentiate crossed ectopia from fused double kidney. In the instance of fused double kidney not only are the pelves reduplicated, but the ureters of each kidney may have separate ureteral orifices If the reduplication is incomplete, however, only a single orifice may be present Occasionally, the ureteral opening of one of the ureters may be extravesicular, rarely, there may be three ureteral orifices on one side of the bladder The fused double kidney appears to be predisposed to hydronephrosis which may be sharply limited to one half of the organ

### Horseshoe Kidney

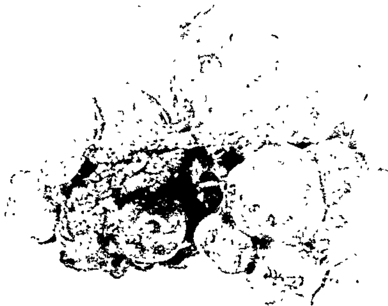
The horseshoe kidney, the "cake" kidney and the L-shaped, or sigmoid kidney all represent essentially variants of the anomaly of median fusion The incidence of horseshoe kidney is variously reported as occurring in from 1 in 715 autopsies to 1 in 376 (Bell) As in other instances, *the overall incidence of anomalies* varies with the proportion of infants in the autopsy sample inasmuch as the frequency of anomalies is considerably greater among stillbirths and the early age groups than in older series (e g horseshoe kidney, 1 in 216 in infants below one year of age) (Bell)

The horseshoe kidneys are believed to result from fusion of the renal blastemas at about the eighth to tenth fetal week, at which time the lower poles of the kidneys are in close proximity Actually, approximately 10 per cent of *horseshoe kidneys are fused at their upper* poles, the remainder being joined at the inferior poles The most common level at which horseshoe kidneys are located is close to the region of the bifurcation of the aorta, between the 3d and 5th lumbar vertebrae; occasionally, they are found at the normal level of the kidney, at the promontory of the sacrum or even in the true pelvis

The long axes of normal kidneys are directed obliquely downward and outward whereas in the horseshoe kidney the axes are directed obliquely inward. As a result, the shadows of calculi in the anomalous kidney are correspondingly situated. The pelves are generally on the anterior aspect of the kidney although often there is no pelvis proper but rather extrarenal calyces which join to form the ureter. The isthmus or site of fusion of the two kidneys may have its own calyx or calyces Reduplication of pelves is not rare The pyramids are arranged in a frontal rather than sagittal plane, so that some of the calyces are directed mesially. In about one third of the cases, there is one artery for each half of the anomalous kidney, in the remainder there are multiple arteries The ureters which usually pass in front of the isthmus, diverge from the midline for a greater distance than normal. This feature may be of diagnostic importance. In some instances, ureters arise from the isthmus The course of the ureter in front of the isthmus, its occasional fixation to that structure, and the frequent presence of accessory vessels are factors predisposing toward obstruction of urinary outflow, and pelvic infection.

*Renal calculi* are more common in the horseshoe kidney than in the normal kidney. They were found in 29 5 per cent of 108 cases (Rathburn); *both pelves were involved in* about 3 per cent of cases There is no specific symptomatology of the horseshoe kidney but the position of this organ tends to produce a clinical entity known as the *Rovsing syndrome* The syndrome is attributed to pressure of the isthmus on underlying abdominal nerves and ves-

A



B



FIGS. A AND B. *Irregular variants of congenitally polycystic kidney* from infants aged six months (figure A) and two weeks (figure B). Both of these cases showed unilateral involvement. The term "multicystic" is often used instead of "polycystic," without special etymologic justification to refer to these irregularly lobulated, misshapen, congenitally cystic kidneys. The photomicrographs of figures A and B are shown in plate 40, and are to be contrasted with those of the usual honeycombed variety of plates 37 and 38.

sels resulting in upper abdominal pain when *standing or sitting, particularly after changing* from a supine position Such patients may learn to lean forward when walking, a position *that effects some relief of pressure from the* isthmus Hyperextension of the back, eating heavily, or lifting may produce exacerbation of *the pain, which, in a few cases, simulates a* tabetic crisis Symphysiotomy or division of the isthmus has given relief in some cases

### Anomalies of Renal Pelvis

The renal pelvis participates, of course, in the *faulty rotation* of the kidney and may lie in any plane from a ventral to a dorsal position As indicated, abnormal rotation occurs in variants of the horseshoe kidney, in double kidneys and in ectopic kidneys The clinical recognition of abnormal rotation is of importance in operations where orientation particularly with regard to anomalous blood vessels is helpful

*Double pelves*

Double pelves occur with a frequency of approximately 1 in 150 autopsies Some authors consider a double pelvis indicative of a double fused kidney in which the isthmus may or may not be evident The double pelves may be associated with complete or incomplete duplication of ureters

*Extrarenal pelves*

These may occur in association with normal kidneys, as well as with horseshoe kidneys, ectopic, hypoplastic and double kidneys The pelvis and calyces are quite clear of the renal parenchyma In some instances, the ureter is formed directly by the union of calyces with the intermediary pelvis The evidence that extrarenal pelves may lead to hypertension is not at all satisfactory.

### Anomalous Renal Vessels

*Anomalous renal vessels* are of importance because of the difficulty they may cause through hemorrhage and infarction by inadvertent tearing or ligation during operations, and because of the ureteral obstruction and hydronephrosis they may produce The anomalies take the form of upper or lower polar arteries from the aorta or the main renal artery, as well as multiple (2, 3 or 4) main renal arteries There is some difference of opinion as to whether or not ligation of a polar artery may be done without hazard It is a fact that ligation of some polar arteries does produce anemic infarcts, so that the size of the vessel and available collateral circulation must be the determining factors Upper polar arteries are found in about one of seven kidneys and lower polar arteries about half as frequently. The lesser incidence of lower polar arteries is fortunate because they, rather than the upper ones, may obstruct the ureters The anomalous vessels are usually accompanied by veins Rarely are the veins present alone, and rarely is a vein responsible for ureteral obstruction The ureter may be obstructed by anomalous vessels at the pelvis proper, at the ureteropelvic junction, and in the lumbar and pelvic portions Nephroptosis is occasionally a contributory factor in the mechanics of ureteral obstruction The symptoms and hydronephrotic effects of arterial compression of a ureter will of course depend on the degree and persistence of occlusion, and the supervention of infection

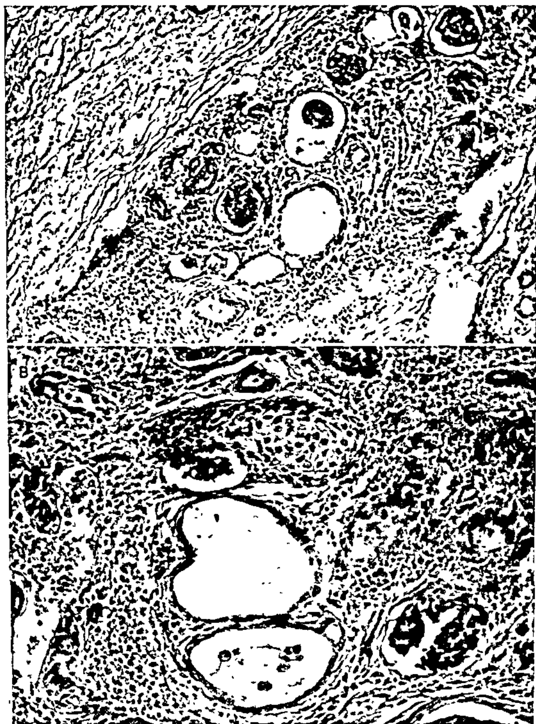
### Classification of Cysts

*Solitary cysts*
- Serous cysts
- Dermoid cysts
- Endometrial cysts
- Parapelvic lymphatic cysts
- Echinococcus cysts

Polycystic
- Congenital
  - Infantile type
  - Adult type
- Acquired (retention cysts of contracted kidney)

Fig A *Congenitally polycystic kidney* illustrated in figure A, plate 39 Much fibrosis is present about more or less complete nephrons in some of which there is the suggestion of partial obstruction

[illegible] B, plate 39 A [illegible] of cartilage (resembling squam- [illegible] figures A and B seems funda- [illegible] in plate 38




(Legends on facing page.)

## Solitary (Simple) Cysts

*Solitary* (simple) cysts of the kidney generally refer to single thin walled, fairly large cysts, averaging 5 to 10 cm in diameter, filled with clear, serous, colorless or light amber fluid and located usually unilaterally at the upper pole in about 23 per cent of the cases, the lower pole in 68 per cent and occasionally in the central portion (8 per cent) (Braasch and Hendrick) (plate 34) Some of the cysts are multiloculated, but the difference is not basic Solitary cysts are found in about 3 to 5 per cent of autopsies, they occur equally between both sexes and are commonest in the group between 35 and 50 years of age. Solitary cysts are rare in infants and children, a fact that suggests the cysts represent an acquired rather than a congenital lesion Solitary cysts may occasionally occur from infarction or traumatic atrophy, and from echinococcus infection.

These cysts are lined by single layered, flat or cubiodal epithelium resembling tubular epithelium The fluid of the serous cyst may contain albumin, leucine, cholesterol from old blood, salts, calcium and traces of urea (plates 34, 316 B) The adjacent parenchyma is compressed and transformed into a fibrous capsule (plates 34, 35)

The cysts are most often clinically dormant although symptoms may arise from pressure, rupture, hemorrhage or infection Hematuria is present in less than 10 per cent of cases (Hinman) Occasionally, the wall of the cyst may become calcified (plate 34 B) and on that account may be visible in a roentgenogram The main differential problem is the distinction of the cysts from neoplasms and hydronephrosis Occasionally, a papillary adenoma arises in a solitary cyst (plate 273).

Multiple small, thin walled serous cysts, averaging 2 to 10 mm are frequently found in gout and in other nephrosclerotic kidneys secondary to arterial and arteriolar sclerosis These are regarded as *retention cysts* with somewhat more conviction than are the large solitary cysts.

*Dermoid cysts* of the kidney occur rarely. (Valentine, 1929, collected eight from the literature and added one of his own ) The n-tain hair, keratin and sebaceous together they resemble the dermoids that arise in other locations, for example, the ovaries They are benign. The dermoid cyst may be grossly simulated by old hemorrhage into a solitary cyst, or by cystic degeneration of an intrarenal encapsulated hematoma in which the old blood has become a grumous mass of cholesterol and hemosiderin (plates 281, 315B)

Only one case of cystic *endometrial* tumor within the kidney has been recorded (Marshall plate 281).* Echinococcus cysts occur rarely in this country but are not uncommon in Australia. *Paranephric cysts* are usually considered to be lymphogenous, some undoubtedly are tubular or pyogenic. They may be simple or multiple (plate 316 A). Further description of the latter three types of cysts is in chapter 14

## Polycystic Kidneys

As with other anomalies the incidence of polycystic kidneys is dependent on the age distribution of the patients autopsied. Combined statistics collected from the literature show an overall incidence of approximately 1 in 350 In 240 stillbirths, the incidence was increased to 1 in 200 (Bell). There is no difference in sex incidence unlike the situation found in bilateral renal agenesia There is a distinct heredito-familial predisposition.

Not all cases of congenital polycystic kidney are bilateral Contrary to the general impression of its infrequency, unilateral polycystic kidneys have been variously reported as occurring in 4 to 13 per cent of cases (Rall and Odel).

The bilaterally involved polycystic kidneys are likely to be of approximately the same size, although occasionally there is considerable difference in their size and weight. As a matter of fact, several examples are revealed in which a large polycystic kidney was removed on the assumption that the opposite kidney was uninvolved because of its normal size; this presumption was proved to be in error when cysts of the remaining kidney enlarged or its polycystic nature was discovered years later On this account clinical data on the incidence

* A sec of endometrial cyst in the kidney w eported (Maslow, L A, and Learner, osis of the Kidney J Urol. 64 56




FIG. A. *Hypoplastic kidney with multiple cysts*, some filled with calcified material.

FIG. B. *Hypoplastic kidney with multiple cysts* of the variety illustrated in plate 39. (A.F.I.P. Acc. 116376.)

Less marked degrees of atrophy of the parenchyma and formation of cysts occur than those indicated above, leaving sufficient parenchyma to carry on normal function. The latter cysts form the subclinical group which survive and which may remain undiagnosed until necropsy (plate 43 B, C) Most of the cysts are filled with thin watery fluid which may be colorless or light yellow, or different shades of brown from old hemorrhage, some contain frank blood or exudate (plate 316B). The lining of the cysts is smooth, except for occasional papillary projections and trabeculations (plate 273), the walls are usually thin, but vary somewhat in thickness, depending on the amount of fibrotic atrophy of the parenchyma about them At the surface, the walls of the cysts are thin enough to be translucent and are easily broken The fluid of the serous cysts contains a high content of urea, uric acid and creatinine, as well as some globulin The correlation with the levels of these substances in the blood requires further documentation The calyces are rather characteristically deformed and elongated This deformity is best observed in molds or in urographic films In advanced cases, the pelvic pattern is bizarre due to the lengthening and compression of the major and minor calyces, so that the term "dragon deformity" is applied to the radiographic picture The normal cupping at the end of the minor calyces may be flattened or expanded The cysts may communicate with the calyces although most do not The polycystic kidney may be associated with other renal anomalies such as double pelvis, double ureters, ectopia, and hamartosis of other organs such as the brain, cord, meninges, skull, vertebral column, liver and pancreas

There appears to be a significant association of polycystic kidneys with polycystic livers (33 per cent) (plate 42), and occasionally with polycystic pancreases (9 per cent) (Rall and Odel)

*Histologic appearance*

The cysts are almost constantly distributed from cortex to medulla, and show no predilection for one part of the kidney except in rare instances as mentioned. The smallest of the cysts are about the diameter of convoluted tubules. They are lined by cuboidal epithelium which is often flattened, so as to resemble endothelium The contents, as a rule, comprise delicate strands and granules of protein precipitate, some of the cysts have dense clumps of acidophilic precipitate, blood, hemosiderin macrophages, calcium deposits and purulent exudate. In a few cysts there are papillary, epithelial covered, fibrous invaginations of the wall. The latter is occasionally thickened by a fibrous rim, apparently the result of parenchymatous atrophy due to expansion of the cysts. The intervening parenchyma varies in amount from case to case and from field to field in the same slide There is nothing characteristic about this parenchyma, and in the regularly polycystic kidney if the parenchyma were viewed apart from the cysts it would be impossible to determine the nature of the basic lesion (plate 43A). This intervening parenchyma is frequently modified by arteriosclerosis and especially arteriolosclerosis in the adult. Glomerulonephritis, pyelonephritis and occasionally even neoplasm may occur just as they may in any other kidney

As mentioned, one form of the infantile polycystic kidney, sometimes referred to as "multicystic" kidney, is composed of markedly irregular cysts and is unilateral. This type shows a histologic picture essentially different from that just described The gross and histologic features are illustrated in plates 39 and 40. In addition to cysts which may vary markedly in size, there are isolated little islands of nephrons in different stages of atrophy, separated by stroma far more abundant than the more usual infantile or adult forms of congenital polycystic kidney. Small bland foci of hyaline cartilage may be seen in relation to these units (plate 40 B) As stated, these unilateral irregularly polycystic kidneys may be markedly diminished in size (plate 41) with much fibrosis, calcification and even ossification and often with rudimentary collecting tubules lined characteristically with tall epithelium (plate 41 B) The ureter of this form of polycystic kidney may be absent or atretic (Goodyear and Beard)




FIG A *Histologic section of congenitally polycystic kidney of adult* demonstrating a moderate amount of parenchyma between the cysts The intervening parenchyma is essentially normal appearing in contrast to that of the infantile "multicystic" kidneys (plates 39 40)

FIG B *Congenitally polycystic kidney of an adult* with abundant parenchyma between cysts Histologic picture in figure C

FIG C *Section of kidney* illustrated in figure B, showing considerable residual parenchyma so that renal insufficiency was averted

*Treatment*

The complications of cystic rupture with perinephritis, the occurrence of hemorrhage or of suppuration in cysts, or the presence of calculi may require major surgery However, the uncomplicated polycystic kidney has been treated by puncturing the cysts with or without marsupialization, injections of sclerosing agents into the cysts, or splitting the kidney down to the calyces The benefits of these forms of therapy are debatable and many prominent urologists are opposed to the use of sclerosing solutions for the cysts In some instances, the function of one of two involved kidneys is poor while the other is adequate In such a situation, nephrectomy of the worse kidney has appeared beneficial, although many urologists oppose this procedure too.

*Embryogenesis*

Two principal competitive theories have been proposed to account for the formation of the cysts According to the theory of Ribbert, the primordium of the secretory or cortical portion of the nephron, after it becomes canalized, fails to join the lumen of the collecting portion which arises separately from ramifications of the ureteral bud It is assumed that the "blind secretory" part of the proximal nephron secretes fluid which is dammed up and results in cystic dilatations

The second theory (McKenna and Kampmeier) postulates that the early generations of secretory tubules, which normally become cystic and disappear, persist, for some reason, to become progressively enlarging cysts The objection to this theory is that these early generations of cysts occur in the zone nearest the medulla and farthest from the ultimate cortical capsule It would therefore be expected that such cysts, if they persisted, would show some corresponding semblance of zonal distribution Actually with few exceptions, the cysts of the polycystic kidneys are equally distributed throughout the kidney

Both of these theories, different as they are, might perhaps be embellished with the additional consideration of the pathogenetic role of defective integration of the inductive influence of Spemann's "organizers" or specialized sentinel cells. And yet, the issue that remains still concerns the histogenesis of the defect and neither of these ingenious but opposing theories quite answers the assignment. For this reason, both enjoy fairly equal popularity despite their disparity

No constructive suggestion is here offered except possibly one based on our somewhat different concept of the embryology of the nephron as outlined in chapter 1. From a study of serial sections of the kidneys of human fetuses from 9 mm. in length to full term size (plates 1–6), the impression is gained that the proximal and collecting portions of the nephron do not develop *pari passu* as two separate tubules with subsequent junction of their lumens into a single tubule, as a pedicle flap might be joined into a receptor site. Rather it is our impression that the tubule from the original ureteral bud elongates, branches and extends into the active multipotent primordial cells of the subcapsular blastema and progressively forms the proximal portion of the nephron from these cells (plate 6) In other words, the glomerulus and proximal tubules are the youngest portion of the nephron not merely because these structures require the stimulus from the collecting tubules to be molded and shortly to be welded to them They are the youngest because, cell by cell, they are built onto the buds of the more distal portions of the nephron advancing into the subcapsular metanephric mass On this account, we believe that the cysts of the polycystic kidney develop not from a failure of the two segments to meet and form a common lumen, but from an atresia or failure of canalization at different levels along the nephron As a result, cysts occur at various levels of the same and different nephrons Congenital atresia is a relatively common phenomenon and probably also occurs in the intrahepatic biliary ducts to cause cysts there, and in the pancreas to produce cysts in that organ The distorted influence of organizers is surely conceded to be the basic fault in the causation of the atresia as it is in other histogenetically unrelated anomalies such as spina bifida, meningocele, anencephaly and others. It is the explanation or structural translation of this influence that is under dispute, as just indicated




FIG. A. *Congenitally polycystic kidney of adult* with suppuration in the cysts. Histologic sections in figures C and D.

FIG. B. *Congenitally polycystic kidneys of an adult* demonstrated by retrograde pyelography.

FIGS. C AND D. *Purulent exudate in cysts of kidney* illustrated in figure A.













Fig A *Congenital hydronephrosis and hydroureter* due to urethral obstruction

Fig B *Congenital hydronephrosis*

Fig C *Congenital hydronephrosis*, hydroureter, double ureter and fused kidneys

Fig D *Congenital hydronephrotic atrophy with hydroureter*

REFERENCES

*Malformations*

BELL, E T Renal Diseases Chapt IV Philadelphia, Lea and Febiger, 1946

BOYDEN, E A Congenital absence of kidney, interpretation based on 10 mm human embryo exhibiting unilateral renal agenesis Anat Rec **52:** 325–349, 1932

CARLSON, H E Supernumerary kidney a summary of fifty-one reported cases J Urol **64:** 224–229, 1950

COLLINS, D C Congenital unilateral renal agenesia Ann Surg **95:** 715–726, 1932

COPPRIDGE, W M Bilateral pelvic kidneys J Urol **32:** 231–235, 1924

EISENDRATH, D N Congenital solitary kidney Ann Surg **79:** 206–228, 1924

——, AND ROLNICK, H C Urology 4th Ed Philadelphia, Lippincott, 1943

EXLEY, M, AND HOTCHKISS, W S Supernumerary kidney with clear cell carcinoma J Urol **51** 569–578, 1944

FORTUNE, C H Pathological and clinical significance of congenital one-sided kidney defect with presentation of three new cases of agenesia and one of aplasia Ann Int Med **1** 377–399, 1927

FRIEDMAN, H H, GRAYZEL, D M, AND LEDERER, M Kidney lesions in stillborn and newborn infants, "congenital glomerulosclerosis." Am J Path **18**: 699–713, 1942

HARRIS, A Crossed renal ectopia without fusion, transperitoneal pyelotomy J Urol **48** 252–255, 1942

HIGBEE, D R Congenital renal hypoplasia with hypertension report of two cases J Urol **51** 466–475, 1944

HINMAN, F The Principles and Practice of Urology Philadelphia, Saunders, 1935

NATION, E F Renal agenesia, a study of thirty cases Surg Gynec & Obst **79** 175–181, 1944

—— Renal aplasia a study of 16 cases J Urol **51** 579–586, 1944

POTTER, E L Bilateral renal agenesis J Pediat **29**: 68–76, 1946

QUINN, W P Case of bilateral renal ectopy J Urol **44**: 10–12, 1940

RATHBURN, N P Notes on clinical aspects of horseshoe kidney J Urol **12:** 611–626, 1924

STEVENS, A R Pelvic single kidneys J Urol **37.** 610–618, 1937

WALTERS, W, AND PRIESTLEY, J B Horseshoe kidney a review of 68 surgical cases J Urol **38** 271–277, 1932

WILMER, H A Unilateral fused kidney, report of 5 cases and review of literature J Urol **40:** 551–571, 1938

*Cysts*

BELL, E T Cystic disease of kidneys Am J Path **11:** 373–418, 1935

BELL, E T Renal Diseases Philadelphia, Lea and Febiger, 1946

BRAASCH, W F, AND HENDRICK, J A Renal cysts, simple and otherwise J Urol **51:** 1–10, 1944

——, AND SCHACHT, F W Pathologic and clinical data concerning polycystic kidney Tr Am A Genito Urin Surgeons **25** 71–87, 1932

FISHBERG, A M Hypertension and Nephritis, Philadelphia, Lea and Febiger, 1939

GOODYEAR, W E AND BEARD, D E Unilateral multicystic kidney in infancy Am J Dis Child **76:** 203–207 1948

HINMAN, F The Principles and Practice of Urology Philadelphia, Saunders, 1935

KAMPMEIER, O F Hitherto unrecognized mode of origin of congenital renal cysts Surg, Gynec & Obst **36**, 208–216 1923

LAMBERT, P P Polycystic disease of kidney, review Arch Path **44:** 34–58, 1947

McKENNA, C M, AND KAMPMEIER, O F A consideration of the development of polycystic kidney Tr Am A Genito Urin Surgeons **26** 377–383, 1933

MARSHALL, V F The occurrence of endometrial tissue in the kidney, case report and discussion J Urol **50**, 652–656, 1943

PIERSOL, G M Polycystic disease of kidneys Ann Int Med **1** 812–818, 1928

RALL, J E, AND ODEL H M Congenital polycystic disease of the kidney, review of the literature and data on 207 cases Am J M Sc **218:** 399–407, 1949

RIBBERT H Ueber die Entwicklung der bleibenden Niere und uber die Entstehung der Cystenniere Verhandl d deutsch path Gesellsch **2**: 187–203, 1900

ROOS, A Polycystic kidney, report of a case studied by reconstruction Am J Dis Child **61**: 116–127, 1941

SCHACHT F W Hypertension in cases of congenital polycystic kidney Arch Int Med **47.** 500–509, 1931

SPEMANN, HANS Embryonic Development and Induction Silliman Memorial Lectures New Haven Yale University Press 1938

VALENTINE J J Dermoid cyst of the kidney Am J Surg **6.** 91–97, 1929

# 6. Diseases of the Glomeruli

## Introduction

Apart *from matters of prevention and therapy*, the problems in glomerulonephritis are concerned not so much with its diagnosis as with the understanding of its natural evolution in terms of physiologic pathology After all, the diagnosis of glomerulonephritis is generally established with relative ease on the basis of hematuria, albuminuria, edema and other adjuvant signs and symptoms But certain key phenomena are unexplained. For example, why does blood escape into the urine in abundance in some cases and not at all in others in which glomeruli seem equally or more damaged? Similarly, what is there about the glomerulitis that causes the urine in some instances of glomerulonephritis to boil solid with albumin while only slight loss of albumin occurs in others? Why is there tubular dysfunction in only a portion of the cases of glomerulonephritis without apparent relationship to the glomerular changes? What mechanisms cause certain kinds of glomerulonephritis to become relentlessly progressive while others are completely resolved? How equivocal is the evidence that "lipoid nephrosis" is really a form of diffuse glomerulonephritis, and is it possible to know merely from histologic examination that the patient's illness was characterized by clinical evidence of the nephrotic syndrome? Are there glomerular lesions which are histologically diagnostic of certain diseases, such as diabetes mellitus, disseminated lupus erythematosus, eclampsia, or subacute bacterial endocarditis?

These are just a few of the central problems that need to be resolved, with at least some help from a tighter clinicopathologic integration Not the least of these problems has been the matter of the pathogenetic significance of edema in disorders of the kidneys Ever since Bright's pioneering realization that "dropsy" and albuminuria were related to renal disease, there has been a lack of agreement on precisely what the relationship was between those cases of nephritis that were predominated by hematuria and renal insufficiency and those marked by little more than persistent edema and albuminuria. Volhard and Fahr believed that the edema represented an involvement of tubules ("nephrosis") which could accompany glomerulonephritis as a nephrotic component ("einschlag") or could occur independently as a tubular disease. This point of view is indicated in the classification published in 1914, in their comprehensive monograph which is remarkable for its crystallization of the information then available.

### Volhard and Fahr's Classification of Bright's Disease 1914

I Degenerative diseases—nephroses—with or without amyloidosis of vessels
- A Acute
- B. Chronic.
- C Endstage—nephrotic contracted kidney without hypertension

Subvariety necrotizing nephroses

II Inflammatory diseases—nephritides
- A Diffuse glomerulonephritis with hypertension
  - 1 acute
  - 2 chronic without insufficiency
  - 3 endstage with insufficiency

  (All three stages can occur with or without a nephrotic component, that is, with severe and diffuse epithelial degeneration ) (Volhard and Fahr)
- B Focal nephritides without hypertension
  - 1 Focal glomerulonephritis
    - a acute
    - b chronic.
  - 2 Septic interstitial nephritis
  - 3 Embolic focal nephritis.

III Arteriosclerotic diseases. scleroses

Benign nephrosclerosis

Combination form· malignant contracted kidney—sclerosis plus nephritis )

Because of his belief, shared by many, that "it is not possible to diagnose accurately, during life, the anatomic changes that will be found in the kidney after death," Christian, in 1925, felt justified in proposing a simple classification unencumbered with histologic segregations, and based primarily on the presence or absence of edema

### Christian's Classification of Bright's Disease

A Acute nephritis
B Subacute nephritis
  1 Subacute nephritis with edema
  2 Hemorrhagic nephritis
C. Chronic nephritis.
  1. Chronic nephritis with edema
  2 Chronic nephritis without edema
  3 Vascular hypertension progressing into nephritis.

Although there are fairly obvious objections to this classification, it did lay stress in an unmistakable manner on at least the clinically different evolution of the disease with and without protracted edema This mode of thought has recently been given by Ellis, to at least some degree, the kind of sound histologic footing that Christian disavowed Ellis sharply separates diffuse glomerulonephritis into two groups: type 1 characterized by known preceding infection, hematuria, azotemia, hypertension and a high percentage of recovery, and type 2 ("lipoid nephrosis") with protracted and abundant edema following insidious onset, and recovery in a very few cases As will be shown, this rigid division into these two types fails to take into account the frequent transition of type 2 into type 1 However, as indicated, Ellis' contribution is his emphasis of the correlation of these clinical types with the histologic changes in the glomeruli

### Current Classification

Our own observations indicate an even greater pathologic correlation of the forms of glomerulonephritis with, and without, edema However, there is, in addition, a more or less specific clinicopathologic quality to other varieties of glomerular lesions which, accordingly, would seem to merit incorporation into a classification of glomerular diseases

In the construction of any classification, the aim, of course, is to achieve a consistent unitarian basis for a systematic arrangement However, it is often not possible to attain this objective The reason is obviously that the information available does not permit the comparable categorization of all diseases on the same plane Therefore, limitations in a classification arise if some of the diseases are arranged according to etiology, others by their clinical symptoms, and still others by anatomical features In the schemes used in this text, morphology has been made the dominant key throughout Where it is required, further definition has been added by compounding the pivotal morphologic disorder with ancillary indications of etiology or duration

### Classification of Glomerular Diseases

Diffuse
  Acute
    Proliferative
    Exudative
    Necrotizing
    Hemorrhagic
    Membranous (e.g., toxemia of pregnancy)
  Subacute
  Chronic
    Sclerosing
    Membranous (with edema) } "lipoid nephrosis"
    Lobular (with edema) }
Focal
  Inflammatory
    Specific
      "Wire-loop" glomerulonephritis of disseminated lupus erythematosus
      Focal endocarditic glomerulonephritis (so-called "embolic")
    Nonspecific
      Focal nonsuppurative glomerulonephritis
      Focal suppurative glomerulonephritis
  Degenerative
    Diabetic glomerulosclerosis
    Amyloidotic glomerulosclerosis
    Argyrosis
Functional (benign albuminuria)

Diabetic glomerulosclerosis and renal amyloidosis are not generally regarded as glomerular diseases, but their glomerular dominance from both the histologic and functional viewpoints appears to justify a reconsideration of their nature, as will be indicated However, for purposes of convenience, they will be discussed under "Vascular Diseases," in terms of capillary (albeit glomerular) sclerosis

### Acute Diffuse Glomerulonephritis

#### *General Features*

*Etiology*

Most cases of acute diffuse glomerulonephritis are generally regarded as complications of a current focus of infection or one that has oc-

curred in the past in any of a number of organs, and has left an altered immunologic status. For example, glomerulonephritis may follow scarlet fever, pneumonia, mastoiditis, osteomyelitis, or bacterial endocarditis The infection preceding glomerulonephritis is likely to be "deep" in contrast to the usual superficial pharyngitis *preceding the onset of rheumatic fever* (Seegal and Earle) The demonstration of a focus of infection can be established more often in children than in adults, and much less commonly in glomerulonephritis with persistent edema ("lipoid nephrosis") than in "hemorrhagic glomerulonephritis" It is extremely *difficult to be certain of the frequency with* which glomerulonephritis complicates infections, because, undoubtedly, many of the milder cases are overlooked Evidence for this conclusion is derived from the fact that, in instances of fatal inflammatory conditions, such as bacterial endocarditis (Bell), ulcerative colitis (Jensen et al ), and rickettsial diseases (Allen and Spitz), a mild, at least histologically demonstrable glomerulonephritis may be found in 50 to 75 per cent of cases In addition, acute glomerulonephritis may be confused clinically with focal glomerulonephritis which, too, may follow infections Although the association of nephritis and focal infection is established, there are several predisposing factors, including age and sex, exposure to cold, familial disposition and immunologic status

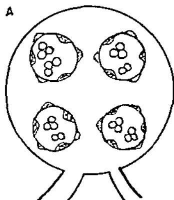
Of the bacteria concerned in the production of glomerulonephritis, the varieties of streptococci play the preponderant role Infections by the gonococcus, meningococcus, pneumococcus and influenza bacillus are less frequent concomitants of acute diffuse glomerulonephritis It is of interest that there is no positive relation between the virulence of the streptococci and the occurrence of glomerulonephritis. It is of additional interest in this regard that geographic areas, such as Puerto Rico, may have an incidence of glomerulonephritis equal to that of more northern latitudes, in contrast to the relatively few cases of rheumatic fever in Puerto Rico Viruses (Herbut) and rickettsias, as indicated, may also be pathogenetically related to diffuse glomerulonephritis. In this connection, it should be mentioned that acute rheumatic carditis is infrequently associated with acute diffuse glomerulonephritis. On the other hand, chronic rheumatic endocarditis offers no special immunity against glomerulonephritis.

*Pathogenesis*

The mechanism by which these agents—the bacteria, viruses, and rickettsias—bring about a glomerulonephritis is by no means clear. The bulk of the evidence suggests that they produce glomerular alterations not *through their direct action on the glomerular* capillaries, but indirectly, probably through the mediation of altered tissue reactivity, hypersensitivity, or some other form of antigen-immune body reactions The following all point to hypersensitivity as an important factor in the genesis of diffuse glomerulonephritis: the occurrence of glomerulonephritis during *convalescence* from an infection such as scarlet fever or tonsillitis, rather than at its height, the presence of fairly uniform, diffuse glomerular lesions; the frequent association of glomerulonephritis with outspoken clinical manifestations of serum sickness or allergy, the increased cutaneous reactivity of patients with glomerulonephritis to filtrates of hemolytic streptococci; the development of high antistreptolysin titers; and the experimental evidence based on the use of antikidney serum as well as repeated injections of globulin In this same connection, it is well to emphasize that the basic phenomena of allergy apply to viruses and rickettsias just as they do to bacteria.

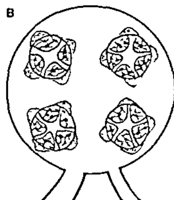
The reactions to the proteid products of bacteria, viruses and rickettsias are not the only means by which glomerulonephritis is caused in the human. We have observed acute diffuse proliferative glomerulonephritis in some instances of chemical poisonings (for example, mercuric chloride) and occasionally following the use of nitrogen mustards in the therapy of cancer Possibly other allergic mechanisms, in which haptene-like linkages of

A



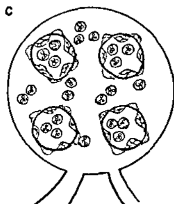
Normal Glomerulus

B



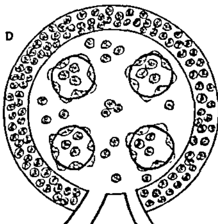
Acute Proliferative Glomerulonephritis

C



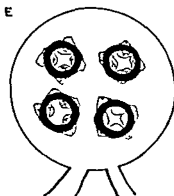
Acute Exudative Glomerulonephritis

D



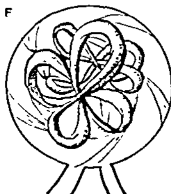
Acute Exudative Glomerulonephritis with Periglomerular Lymphangitis

E



Acute Membranous Glomerulonephritis

F



Acute Necrotizing Glomerulonephritis




FIG A *Acute diffuse proliferative glomerulonephritis* showing marked dilatation of Bowman's *space with abundant protein precipitate from permeable only moderately cellular glomerular capillaries* Homogeneous grey-black casts are in distal convoluted tubules with only loose granular precipitate in proximal convoluted tubules (A F I P Acc 101695)

FIG B *Acute diffuse*
glomeruli from kidney
ticularly of endothelial
disruption of glomerular architecture, fusion of glomerular loops and transuded protein precipitate in Bowman's space Note too the fibrinoid degeneration of Bowman's capsule

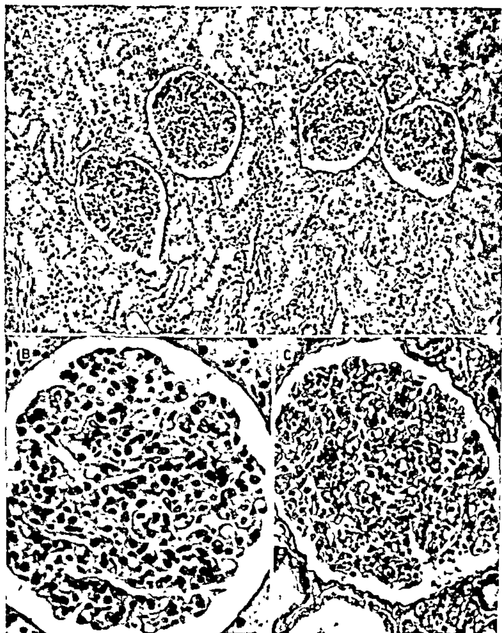



FIG A *Acute diffuse proliferative glomerulonephritis*, characterized by ischemic glomeruli that are larger than normal and have an obviously increased cellularity The tubules appear uninvolved despite the glomerular ischemia

FIG B *Acute diffuse proliferative glomerulonephritis* A higher magnification of a glomerulus from kidney illustrated in figure A Note the increased numbers of large hyperchromatic endothelial cells and the moderately swollen capillary basement membrane

FIG C *Silver stain* of glomerulus from acute diffuse proliferative glomerulonephritis with no significant histologically discernible alteration in the basement membrane Nevertheless this patient died of renal insufficiency

nonbacterial proteins participate, are responsible for some cases of glomerulonephritis in the absence of infection. More recently, it appears that stresses of various sorts with the altered response to corticones potentiated by sodium salts may be another pathogenetic facet in the evolution of glomerulonephritis (Selye)

*Experimental Glomerulonephritis*

If acute diffuse glomerulonephritis in humans occurs as a result of a hypersensitive reaction to the products of bacteria, rickettsias and viruses, it is a remarkable fact that spontaneous *diffuse glomerulonephritis is relatively* rare in animals (plate 60) Surely this fact is not dependent on the absence of spontaneous infections in animals Experimentally, acute diffuse glomerulonephritis has been reported following the injection of bacteria or their products (Duval and Hibbard; Lukens and Longcope), the production of brucellosis (Margolis et al ), the use of foreign proteins (More and Waugh), and the administration of specific antirenal antibodies after the methods of Masugi (Schwentker and Comploier, Smadel; Kay) Of all the procedures used, none has yielded histologic pictures that so closely simulate the spontaneous disease of humans as have the last two methods. the use of repeated injections of gamma globulin and the use of antikidney antibodies Both of these types of studies suggest an underlying allergic pathogenesis It is of interest that interference with renal function by unilateral ligation of the ureter tends to inhibit glomerular alteration in the ipsolateral kidney in contrast to the glomerulonephritic changes produced in the opposite kidney by the Masugi procedure (Reubi).

*Clinical Picture of Acute Diffuse Glomerulonephritis*

Acute diffuse glomerulonephritis may occur at any age, but about 70 per cent begin in the cut example of acute diffuse glomerulonephri- period between 5 and 20 years of age A clear tis was reported in a 2 months old infant (Yampolsky and Mullins). Unlike the situation in chronic pyelonephritis, acute glomerulonephritis is noted about twice as commonly in males as in females. In contrast, the incidence of rheumatic fever is about equal in the two sexes Occasionally, siblings of families contract the disease almost simultaneously, an occurrence which Addis has regarded as probably signifying a familial predisposition. Whether or not this truly represents some constitutional predisposition or a vulnerability because of similar immunologic behavior, or merely an expected reaction to similar organisms in a similar over all environment, is not clear.

The clinical picture of acute glomerulonephritis may vary from merely the presence of proteinuria as detected in routine examinations, to the full blown clinical picture, including uremia, hypertensive encephalopathy and cardiovascular manifestations; hypertensive neuroretinopathy occurs rarely. The initial phase usually lasts several weeks, but may range from a few days, terminating in resolution or death, to as long as several months

The signs and symptoms include pallor of the skin, moderate fever, lumbar pain, radiating downward, urgency and frequency of micturition, nocturia, chills, headache, nausea and vomiting, and edema of the eyelids, face and genitalia, as well as of the sacrum in the bedridden. The edema is not the result of generalized capillary damage, but is, on the basis of cardiac failure, and/or osmotic changes in the blood, due to renal damage The protein content of the edema fluid is comparable to or less than that of edema fluid in cardiac failure (Warren and Stead).

The initial symptoms, especially in children, may be cerebral and may be mistaken for encephalitis. Cardiac insufficiency, some degree of which is present in about 75 per cent of clinically apparent cases, occasionally dominates the clinical picture and may be so striking that the cardiac edema may be erroneously considered of renal origin. Despite the pallor, only a mild degree of anemia is noted, as a rule, in the early stages.

The rise in blood pressure usually affects both the diastolic and systolic levels, but the

PLATE 49. ACUTE DIFFUSE EXUDATIVE GLOMERULONEPHRITIS

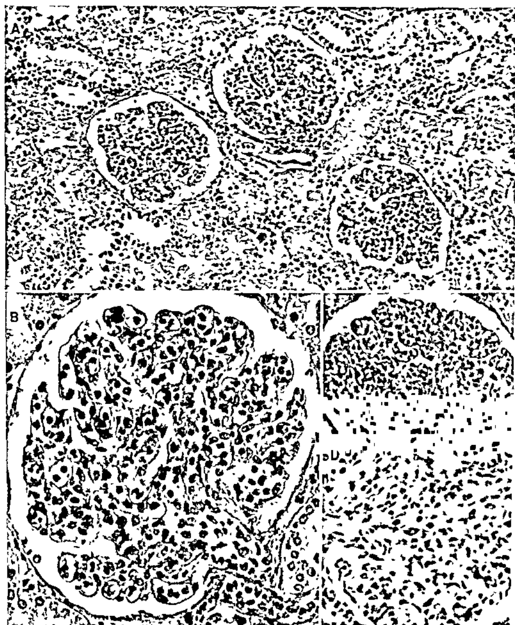



FIG A *Acute diffuse exudative glomerulonephritis* The glomeruli are enlarged, ischemic and excessively cellular Again, the tubular epithelium is not especially altered, despite the glomerular ischemia

FIG B *Acute diffuse exudative glomerulonephritis* A higher magnification of glomerulus from kidney of figure A This is the *exudative* type of glomerulonephritis with polymorphonuclear leukocytes confined in this early stage to the lumens of capillaries

FIGS C AND D *Acute diffuse glomerulonephritis* showing combined features of proliferation and exudation




FIGS A AND B *Trench nephritis* showing the swollen moist cortex and congestion common in banal forms of acute diffuse glomerulonephritis The surface is mottled by stellate veins(*A*).

FIG C *Trench nephritis* with a histological picture of the combined exudative and proliferative types The glomeruli are considerably enlarged, cellular and ischemic; nevertheless, the tubules are intact, an association that is not uncommon, thereby indicating that serious compromise of the glomeruli need not produce histologically evident tubular alteration

systolic pressure alone may be elevated, especially at first. In adults, the usual elevation is between 130 and 170 mm, pressures over 200 mm are unusual In some cases, especially in adults, dyspnea is the prominent symptom and is the result of acute myocardial failure. This was the common picture in trench nephritis, and is a serious prognostic sign, presaging death in the acute stage Epistaxis, purpura and thrombopenia may also occur

*Laboratory Data*

The urinary volume may be diminished to the point of anuria in the severest cases The oliguria averages 400 to 600 cc daily and if severe tubular damage is present, the specific gravity of the urine is low and fixed If the oliguria is due in large measure to cardiac insufficiency, or other prerenal deviation of water such as might occur from vomiting, then the specific gravity is elevated This feature is of some differential importance in the diagnosis of renal versus extrarenal origin of oliguria, although in practice, it is not nearly as clear cut as it might seem inasmuch as tubular reabsorptive capacity is not diminished in all cases of acute glomerulonephritis

In acute diffuse glomerulonephritis, the urine practically always contains blood, protein and casts The hematuria may be evident on gross examination of the urine which appears "smoky," or coffee colored Actually, as Addis points out, it takes only a drop or two of blood, about 0 2 cc, to produce this discoloration of the urine The degree of hematuria is not necessarily an indication of the severity or prognosis of the disease Certainly there is no correlation between the amount of hematuria and the extent of histologically evident glomerular damage In most cases, hematuria tapers off after a few days or weeks, but a few red blood cells may escape into the urine for months, again without reflection of the prognosis. The erythrocytes may be hemolyzed in their passage through the kidney (plate 55) so that hemoglobinuria may also be present

As stated, proteinuria is rarely absent in acute diffuse glomerulonephritis It usually is of the order of 0 3 per cent, but may exceptionally exceed 2 per cent Here, too, the severity of the disease need not parallel the level of albuminuria although if the excretion of albumin is protracted and abundant, the nephrotic syndrome and its attendant perils may be anticipated

Casts are also almost a constant part of the picture in acute diffuse glomerulonephritis Early, there are hyaline and epithelial casts predominantly, later, epithelial and granular casts, cylindroids and rarely waxy casts may be added Polymorphonuclear leukocytes are present in moderate numbers and tubular epithelial cells are found in the later periods Incidentally, in evaluating the degree of proteinuria, the sediment should be taken into account, for example, 100,000 white blood cells in 2 cc of urine add 0 1 Gm of protein

The sedimentation rate of the red blood cells is often elevated in acute diffuse glomerulonephritis as are the titers of antistreptolysin and antistreptokinase

Fatal impairment of renal function in acute diffuse glomerulonephritis does occur but it is a relatively uncommon occurrence Death, in this acute stage, may result from cardiac failure Oftentimes, as a result of prerenal deviation of fluid, there is a disparity between the minor degree of renal impairment and the marked azotemia in acute glomerulonephritis In such cases, the phenolsulfonphthalein test may show an excretion of somewhere around 10 per cent in two hours, despite the lack of appreciable renal dysfunction

*Clinical Evolution of Acute Diffuse Glomerulonephritis*

The answer to the question, "What percentage of patients with acute diffuse glomerulonephritis recovers completely?" depends on whether the clinically evident or the histologically evident disease is meant As has already been stated, in a variety of infections, or, at least, inflammatory diseases, histologically documentable acute diffuse glomerulonephritis occurs in from 50 to 75 per cent of patients These lesions are of the exudative and/or proliferative types, rarely of the necrotizing




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FIG A *Trench nephritis* characterized by acute diffuse proliferative and exudative glomerulonephritis

FIG B *Mitotic figure* (arrow) in endothelial cell of glomerulus of acute diffuse glomerulonephritis in trench nephritis




FIG A *Exudative type of acute diffuse glomerulonephritis* produced in this case by toxicity to *sulfathiazole* and characterized by polymorphonuclear leukocytes in glomerular capillaries, Bowman's space and periglomerular lymphatics (Compare plate 46D)

FIG B *Exudative and proliferative type* of acute diffuse glomerulonephritis Note exudation of polymorphonuclear leukocytes, proliferation of endothelial cells and ischemia

type Therefore it would be expected that if the patient had recovered from the primary illness —for example, subacute bacterial endocarditis, typhus fever, or ulcerative colitis—then, with few exceptions, the glomerulonephritis would have healed In most of these cases, the glomerulonephritis is not recognized clinically, although, in retrospect, there is usually adequate basis for the diagnosis. Hence, to return to the original question, if such less overt forms of glomerulonephritis are included in the sample, it is of further interest to learn th of *all* the glomerulonephritic patients seen Addis' clinic, 52 per cent died of their ren disease, and 48 per cent recovered. These a patients who were referred to the clinic various stages of their disease. Many of th patients were already "on their way to deat when first seen, so that, again, the number fatalities is large. The course of acute diffu glomerulonephritis as represented by Addis shown in figure 1.

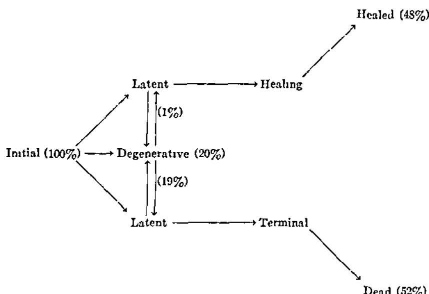



Fig 1. Course of *Clinically Evident* Acute Glomerulonephritis (From Addis *Glomerular Nephritis*, Ne York, The Macmillan Co, 1948)

sample, the answer is that a very small percentage—perhaps several per cent—of cases of acute diffuse glomerulonephritis die of renal failure

On the other hand, of those patients with acute diffuse glomerulonephritis who are seen in the *acute* stage at a *nephritis clinic*, fully 20 per cent expire as a direct result of the renal insufficiency, and the remainder, 80 per cent, recover from the renal disease (Addis). However, these are patients who have been referred to a famous clinic for kidney disorders, so that it is obvious, as Addis notes, that the statistical sample is not representative of the over-all "nephritic population" The percentage of recoveries in the latter group would undoubtedly be greater than 80 per cent. Despite the acknowledged selectivity of the

According to the definitions of Addis, the in itial phase is characterized by coffee-colore urine, edema and hypertension; the laten stage, beginning within a month after the onse of the disease, is identified merely by an abnormal urinary sediment; the degenerativ stage is the clinical nephrotic syndrome.

Exceptionally, as indicated, death occurs from renal failure during the acute stage of the disease (plates 47–55) As a rule, the patient recovers Of 88 such healed cases, 81 8 per cent recovered within two years, 5 7 per cent took 6 to 10 years (Addis). In the minority of cases, then, there is evolved the picture of subacute or chronic glomerulonephritis after more or less of a latent stage in some instances Cases of apparently completely healed acute diffuse glomerulonephritis rarely relapse. The chronic

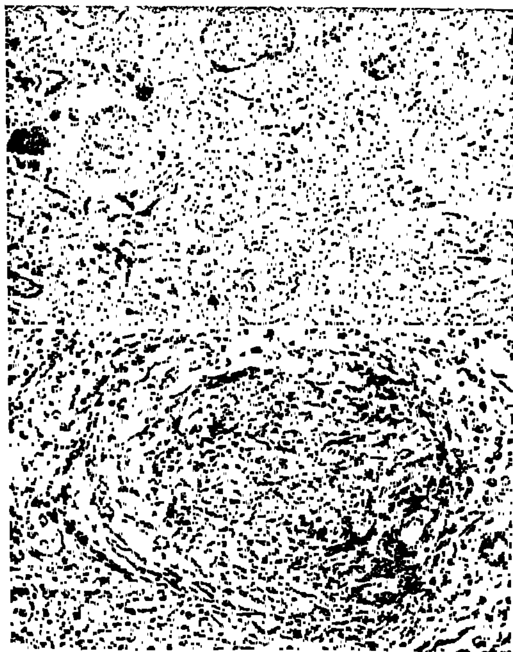


FIG A *Necrotizing type* of acute diffuse glomerulonephritis characterized by exudation of polymorphonuclear leukocytes, disruption of glomerular architecture, glomerular ischemia and fibrinoid necrosis of capillary walls. Note blood in distal tubules

FIG B *Exudation, fibrinoid degeneration and thrombosis* of glomerular capillaries in acute diffuse necrotizing glomerulonephritis. It is clear that such gnarled glomeruli cannot be restored to normal, unlike those of proliferative or exudative glomerulonephritis

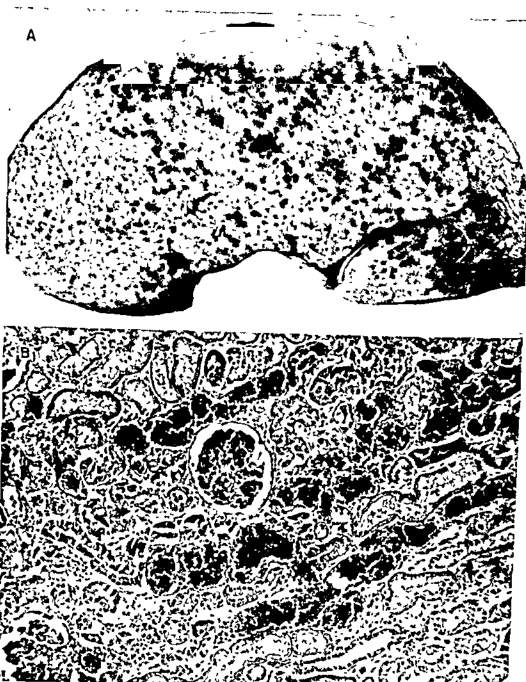



FIG A *Acute diffuse hemorrhagic glomerulonephritis* showing the numerous cortical flecks of blood corresponding to the blood in the tubules as shown in figure B Grossly, this kidney also resembles that of focal endocarditic glomerulonephritis (plate 85A) and malignant nephrosclerosis (plate 211A)

FIG B This photomicrograph is of a section taken from kidney illustrated in figure A Masses of red blood cells are in the distal nephron The proximal nephrons are free of blood The representative glomerulus illustrates the thromboses characterizing this lesion and the relatively minimal additional glomerular alteration that is often present in this variety of glomerulonephritis (further shown in plate 55A)

phase may be a continuous and rapid progression of the acute stage with death in uremia in a few weeks or months, or there may be a variable dormant period with inconstant amounts of slight to moderate proteinuria as the only manifestation of the disease This type may remain latent or finally develop one or other of the clinical variants of chronic glomerulonephritis to be described in the section on that topic. Another group may escape the acute phase merely with hypertension Some cases actually develop the phase of accelerated or malignant hypertension Still others, the recurrent type, develop repeated acute attacks of glomerulonephritis, usually followed eventually by renal insufficiency

Finally, there is yet another, prognostically grave group which is predominated by a persistent abundant albuminuria and edema, although infrequently this type may be initiated with the signs of a hemorrhagic glomerulonephritis (Schwarz et al ). In many of these instances, the fatal termination is the result of secondary infection, in some, there is ultimate progression to hypertension and renal insufficiency. This is the hitherto controversial category of cases which has in the past been called "lipoid nephrosis," but for clinicopathologic reasons to be outlined, clearly appears to be a variant of diffuse glomerulonephritis, either of the membranous or lobular types (plates 73–80)

### *Prognostic Factors*

There is no way of making certain what the outcome of an attack of acute diffuse glomerulonephritis will be There is suggestive evidence that adequate therapy with penicillin *early* in the course of the disease—that is, within the first days—reduces the severity (but not the incidence) of glomerulonephritis and its sequelae (Weinstein et al ) Certain data, however, do furnish presumptive prognostic clues The clinical severity of the initial attack is not necessarily an indication of the future tempo of evolution of the disease In some of the severest cases, recovery has occurred within the first year However, the presence of hypertension and renal impairment for more than a few months after the onset, makes complete recovery highly unlikely In those cases with marked albuminuria and edema, the additional feature of hypertension adds a serious increment to the gravity of the prognosis In general, the prognosis varies with the height of the blood pressure, especially the diastolic pressure Hypertensive neuroretinopathy, epileptiform convulsions and other signs of hypertensive encephalopathy are ominous Another guide to the progress of the condition is the trend in the capacity to concentrate the urine The specific gravity, even of routine morning specimens of urine over a period of weeks or months is likely to reflect the deterioration of the kidney by the trend of progressive lowering of the specific gravity In the absence of any indication of progression of the disease, even though hypertension, proteinuria and some edema may exist, the capacity to live normal lives may be retained for years However, such patients remain vulnerable to sudden relapse from intercurrent infection, cardiac failure or pregnancy

## General Features of Pathology of Acute Diffuse Glomerulonephritis

### *Gross Appearance*

In the very early or mild cases, there may be no demonstrable gross changes As a rule, however, the kidneys are enlarged from one and one-half to twice normal size The capsules may be stripped easily, disclosing a smooth surface which is deep purplish-brown or a pale greyish-brown, depending on the state of congestion (plates 50 A, B) The surface is usually reddish, smooth and may be dotted with fine punctate hemorrhages The cut surface may be pale yellowish-grey, but is often moist and deep red The cortex and medulla are fairly sharply differentiated The pyramids are markedly congested and because of the red streaks of hyperemic vasa recta may grossly simulate a hemoglobinuric nephrosis, indeed, blood or hemoglobin may actually be present in the tubules, so as to add to the red radial striae On careful examination with the naked eye, the glomeruli characteristically are more prominent than normally and are visible as fine, whitish dots—whitish because of the ischemia and cellular




FIG A In this instance, there is acute proliferative glomerulitis with red blood cells principally in the proximal nephron, no blood is present in Bowman's space

FIG B *Acute diffuse hemorrhagic glomerulonephritis* from the same case illustrated in figure A Red blood cells and hemoglobin (from laked tubular blood) are present in the distal tubules, and may be mistaken for hemoglobinuric (lower nephron) nephrosis




FIG A *Hydropic vacuolated epithelium* of proximal convoluted tubules in acute diffuse proliferative and exudative glomerulonephritis This vacuolated change is attributed to changes in oncotic pressure very much as in hypertonic sucrose nephrosis in which the epithelial change is identical

FIG B *Proximal tubular epithelial necrosis and regeneration* in acute diffuse proliferative glomerulonephritis

FIG C *Flattened, elongated, hyperchromatic, regenerating epithelial cell* (arrow) of proximal tubule in acute proliferative glomerulonephritis

proliferation However, in some instances they are distinctly red because of intraglomerular hemorrhages or congestion, in still others, they may be hidden from view by swollen adjacent parenchyma

### *Histologic Appearance*

*Glomeruli*

The histologic changes of acute diffuse glomerulonephritis do not conform to a single standard prototype The picture varies considerably The pathogenetic basis for the variable histologic response is obscure, but it would seem likely that these morphologic alterations are an expression of the degree of the allergo-immunologic reaction rather than of the difference in the various provocative agents. These agents may be drugs, bacteria, rickettsias, viruses or their antigenic products, the histologic effects of which are modified by the state of reactivity of the renal tissue.

The changes are essentially a diffuse glomerular capillaritis The inflammation of the loops may take the form of swelling, hyperchromatism and proliferation of the fixed cellular elements, thickening, reduplication and granular fibrinoid alteration of the capillary basement membrane with or without glomerular thromboses, the accumulation of polymorphonuclear leukocytes, both intra- and extravascularly, gnarled distortion of the glomerular capillaries, and finally, a combination of any of these changes

From the functional viewpoint, the most important histologically visible result is glomerular ischemia and evidence of interference with glomerular blood flow and glomerular filtration. Less obvious changes leading to abnormal permeability of the glomerular capillaries may occur. In many cases, the degree of altered glomerular permeability is not apparent from the histologic sections, but in the membranous and lobular glomerulonephritis to be described, a mere examination of the sections yields this information (plates 73–80).

*Tubules*

The physiologic evaluation of the tubular change in acute diffuse glomerulonephritis is an exceedingly difficult problem. Contrary to what might be anticipated, there is no direct correlation between the degree of glomerular and tubular changes, even though it is generally assumed that the tubular damage is secondary to the compromise of their blood supply by glomerular ischemia. Actually, the epithelium of the tubules may be histologically unaltered, notwithstanding acute glomerular change, so that the concentrating ability of the kidney is unimpaired. On the other hand, the tubular epithelium, particularly that of the proximal nephron, may be vacuolated with lipid or fluid (plates 56, 66), may contain huge hyaline granules (plate 75 C), or may be so necrotic as to suggest a primary necrotizing tubular disease (plate 56 B, C). The variable extent of this damage is the reason for the variable tubular function in glomerulonephritis, especially as revealed by the specific gravity of the urine

The individual histologic forms of glomerulonephritis (plate 46) are considered in the following sections.

### Acute Diffuse Proliferative Glomerulonephritis

Acute proliferative glomerulonephritis is characterized by diffuse involvement of glomeruli with hyperplasia and swelling principally of the endothelial cells and to a lesser extent of the epithelial cells (plates 47, 48) The increase in size of the individual cells involves the nuclei particularly. The lumens of the glomerular capillaries tend to be ischemic. The basement membrane typically is histologically unaltered, in this form, although some observers require that the basement membrane be altered before the diagnosis of glomerulonephritis is made Bowman's space tends to be narrowed by the enlarged malpighian tufts, Bowman's capsule is usually unchanged, but occasionally shows a segmental fibrinoid swelling (plate 169 B). The extraglomerular vessels are not remarkable. As a rule, there is no associated interstitial inflammation. Isolated hemoglobin casts may be found in loops of the distal convoluted tubules situated near the glomerulus; the medullary tubules are spared The epithelium of the tubules shows no changes of note although sometimes the epithelium of the

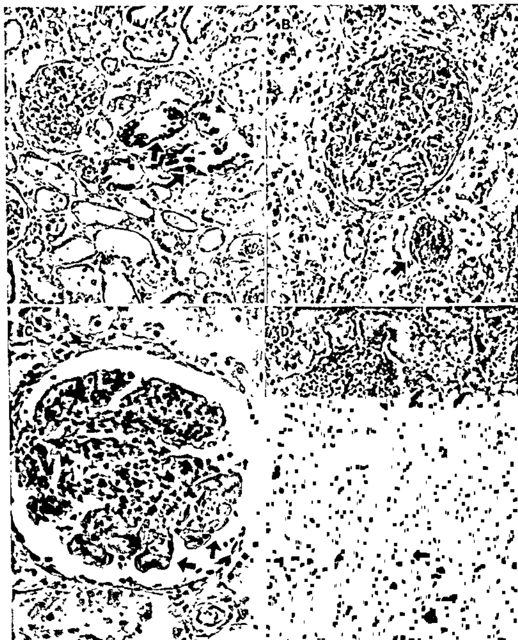



FIG A *Acute diffuse proliferative glomerulonephritis* attributed to a nitrogen mustard (SK1195) The dark luminal masses (arrows) represent calcification of necrotic epithelium of proximal tubules

FIG C *Acute diffuse proliferative glomerulonephritis* with focal fibrinoid swelling of glomerular capillaries (arrows) similar to the "wire-loop" changes of disseminated lupus erythematosus No other stigmata of lupus erythematosus were present

FIG B *Acute diffuse necrotizing glomerulonephritis* in a patient with fulminant influenzal type of interstitial pneumonitis, associated with marked hematuria A blood cast is seen in a distal convoluted tubule (arrow)

FIG D *Nonspecific acute diffuse exudative and proliferative glomerulonephritis* associated with blastomycotic nephritis Blastomyces (arrow)

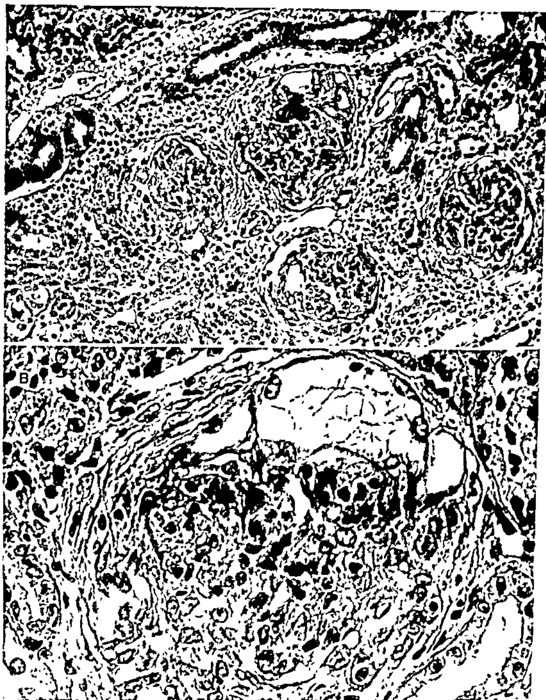



FIG A *Experimental chronic sclerosing glomerulonephritis* produced in rabbits by the injection of bovine serum gamma globulin after unilateral nephrectomy

FIG B *Glomerular alteration* from case of experimental glomerulonephritis illustrated above The crescent, glomerular ischemia, fusion and thickening of capillaries, proteid exudation and the cellular proliferation make this picture indistinguishable from the lesion of human chronic glomerulonephritis (Histologic slides obtained through the courtesy of Dr. R H More )

proximal tubules may show hydropic vacuolization

This form of glomerulonephritis occurs commonly in a variety of infectious and allergic diseases and may be undetected clinically. In view of the retention of basic architecture, it is a reversible type of glomerulonephritis in its early stage, and commonly is completely resolved if the underlying primary disease is cleared.

### Acute Diffuse Exudative Glomerulonephritis

Acute diffuse exudative glomerulonephritis also involves all of the glomeruli and the essential feature is the presence of polymorphonuclear leukocytes within the lumens of the ischemic glomerular capillaries (plate 49). Because the leukocytes are practically confined to the capillary lumens and spare Bowman's space, the lesion may be overlooked and the leukocytes regarded merely as a reflection of their preponderance in the peripheral blood. The leukocytes within the glomeruli may be the only visible change, although not infrequently the exudative glomerulonephritis may be associated with features of the proliferative form, particularly the swelling and hyperplasia of the endothelial cells (plates 49 C, D and 50), changes in the basement membrane and adhesions between loops are usually absent. In extreme cases, the exudate of polymorphonuclear neutrophils may fill not only the lumens of the glomerular capillaries but also Bowman's space and the surrounding periglomerular lymphatic channels (plate 52 A). This type, too, is reversible in its early stage.

### Acute Diffuse Necrotizing Glomerulonephritis

In acute necrotizing glomerulonephritis, there is diffuse involvement of glomeruli characterized by ischemia, patchy, fibrinoid degeneration of glomerular capillary walls, necrosis as well as irregular proliferation of epithelial and endothelial cells, and focal capillary thromboses (plate 53). The fibrinoid alteration may involve also Bowman's capsule and the afferent arterioles. The efferent arterioles seem to be spared. There may be considerable associated interstitial edema and focal infiltrations of lymphocytes, plasma cells and histiocytes. The epithelium of the proximal convoluted tubules may show more or less degeneration beyond the stage of so-called cloudy swelling and may be accompanied by evidence of epithelial regeneration. Loose granular protein precipitate often with intact or partially laked and fragmented red blood cells may be found in Bowman's space and in the lumen of the proximal part of the nephron. The distal nephron may contain hyaline acidophilic casts, and red blood cells in various stages of degeneration, either loose or in casts. All in all, there is generally a marked disparity between the relatively slight tubular changes and the striking glomerular destruction. The prognosis for this type is most serious.

### Acute Diffuse Hemorrhagic Glomerulonephritis

In the kidney of acute diffuse hemorrhagic glomerulonephritis, the most evident change is the presence of large numbers of intact red blood cells dilating Bowman's space and thereafter filling the proximal convoluted tubules. Occasionally, the red blood cells are altogether absent from the proximal nephron and are first seen in the more distal portions of the nephron. In this location, the blood may have been altered into casts of hemoglobin, and on this basis, the lesion confused with hemoglobinuric or lower nephron nephrosis (plates 54, 55). Except for the slight to moderate swelling and proliferation of endothelial cells, the glomeruli may show remarkably little alteration despite the obvious evidence that there has been permeability to red blood cells.

### Acute Membranous Glomerulonephritis

Acute diffuse membranous glomerulonephritis occurs not only in eclampsia, but as the first stage of the chronic membranous glomerulonephritis with edema ("lipoid nephrosis," type 2 of Ellis), and as the stage preceding the late or contracted phase of many of the cases of sclerotic glomerulonephritis that were earlier characterized by abundant edema. In eclampsia, the clinical picture is modified by the gestation, although edema, albuminuria,

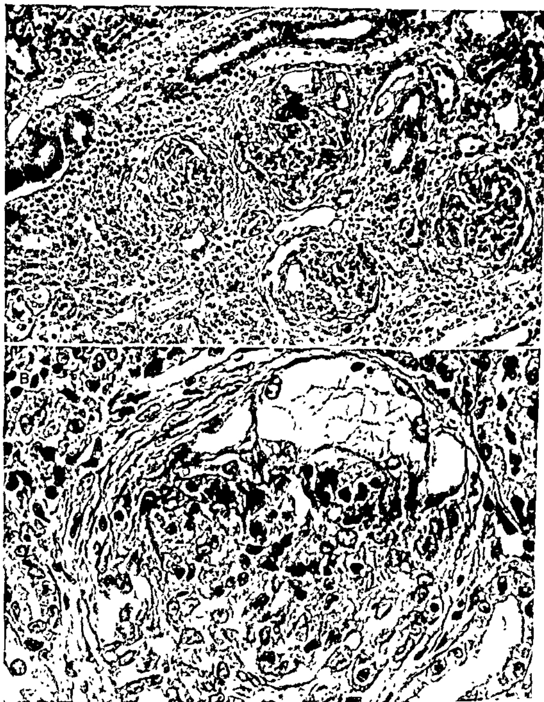



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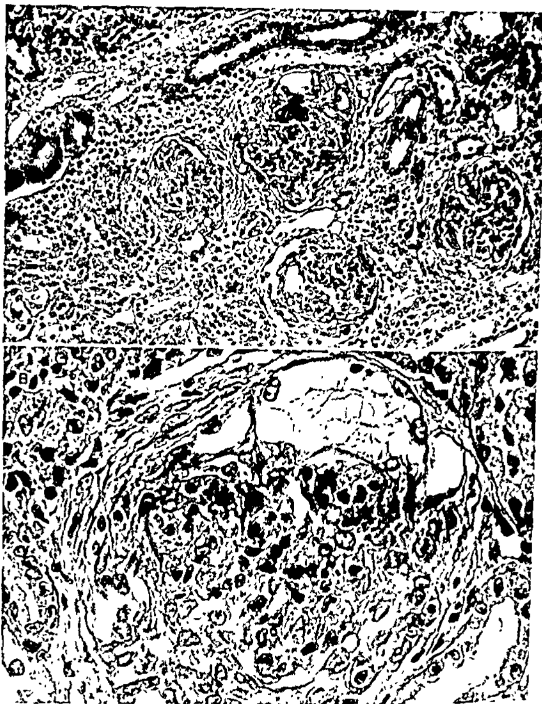



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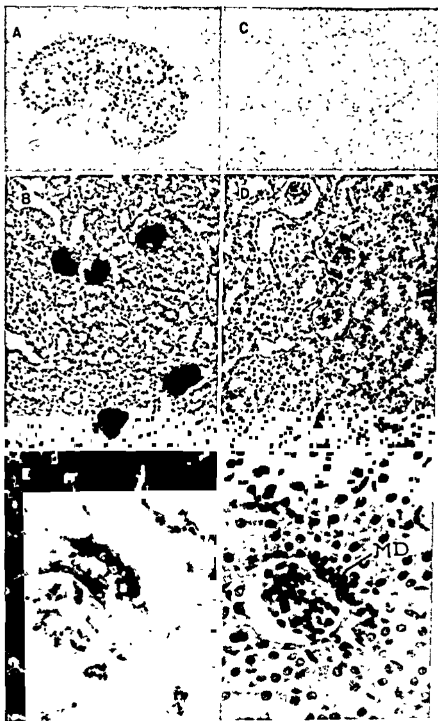
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(Legends on facing page)

and hypoproteinemia, here too, are often a prominent part of the syndrome, as would be anticipated. It appears also likely that the lesion of syphilitic nephrosis is an acute, reversible membranous glomerulonephritis, although the available data do not permit a documented statement on this subject.

*Histology*

The lesion of acute membranous glomerulonephritis is characterized by a soft fibrinoid swelling of the walls of the glomerular capillaries (plate 101). Usually this swelling is quite uniform and diffuse and may be associated with slight to moderate proliferation and swelling, particularly of the glomerular endothelial cells. The lumens of the glomerular capillaries are ischemic and may contain fibrinous thrombi. In many instances there is evidence of a markedly increased permeability of the glomerular capillaries to protein as manifested by the proteid fluid in Bowman's space, at times so abundant as to compress the tuft. In addition, the degenerative and regenerative alterations of the epithelium of the proximal convoluted tubules may be so marked as to be confused with a primary necrotizing tubular disease. It is remarkable that in acute diffuse membranous glomerulonephritis red blood cells are rarely seen in Bowman's space or in the tubules, in contrast to the situation in acute diffuse hemorrhagic glomerulonephritis, notwithstanding the far greater histologic change in the glomerular capillary basement membranes in the former.

SUBACUTE DIFFUSE GLOMERULONEPHRITIS

The designation of "subacute" glomerulonephritis is an arbitrary clinical reference to the disease which has lasted from about three to twelve months. There is questionable nosologic justification for this separate intermediate group, but the histologic changes in the kidneys in these cases are of interest not only because of certain distinctive features, but also in terms of the evolution of the lesions in the more protracted or chronic cases. The patients with subacute glomerulonephritis tend to have abundant albuminuria, often in association with edema, hypoproteinemia, hypercholesterolemia, moderate hypertension and anemia. Terminal renal insufficiency with oliguria and urine of low specific gravity because of the tubular damage are the rule.

*Pathologic Anatomy of Subacute Diffuse Glomerulonephritis*

The kidneys of subacute diffuse glomerulonephritis are not contracted, but are usually larger than normal and have pale or greyish-yellow smooth surfaces. Many are grossly quite like those of so-called "lipoid nephrosis", the reasons for this are understandable in view of the clinical picture. Subacute glomerulonephritis, therefore, is what was formerly called the "large white kidney," in contrast to the "small white kidney" of the third or chronic stage of glomerulonephritis, and in contrast to the "red" kidneys of arteriolar nephrosclerosis. Other names are still occasionally retained to signify subacute glomerulonephritis, these names include subchronic nephritis, glomerulotubular nephritis and diffuse parenchymatous nephritis.

*Histologic Types of Subacute Diffuse Glomerulonephritis*

Histologically three essential patterns of glomerular change occur although it appears

FIGS. A AND B. *Radioautographs* of kidneys of a mouse injected with radio-anti-mouse-kidney serum showing a selective concentration of radioactivity in the glomeruli. (Exposure on Ansco No screen x ray film.)

FIGS. C AND D. *Control radioautographs* of the entire kidney and a histologic section from a mouse which received radio anti mouse kidney serum. There is no evidence of significant radioactivity. (Courtesy of D. Pressman, see Science *109*: 65–66, 49, J. Immunol. *64*: 281–287, 1950.)

FIGS. E AND F. *Fluorescein labeled antiserum* against B. Friedlander. The section (E and F) is from the kidney of a mouse given an intravenous injection of capsular polysaccharide of B. Friedlander 48 hours before being sacrificed. The histologic section, itself, was then treated with the fluorescent antibody and the same field photographed under the fluorescent microscope (E) as well as with visible light (F). The antibody appears concentrated in the macula densa (MD). (Courtesy of Hill, A. G. S., Deane, H. W., and Coons, A. H. J. Exper. Med. *92*: 35–41, 1950.)

PLATE 60 CHRONIC SCLEROSING AND MEMBRANOUS GLOMERULONEPHRITIS OF DOG




FIG A *Spontaneous chronic sclerosing glomerulonephritis of dog* showing diffuse glomerular as well as tubular change The glomerular capillaries are focally scarred but some have walls with diffuse membranous thickening The epithelium of the proximal convoluted tubules is vacuolated by fat as in human cases of chronic nephrotic glomerulonephritis.

FIG B *Markedly scarred glomerulus* from case illustrated above.

FIG C *Two glomeruli*, one with its capillaries practically obliterated, the other with focal fibrosis

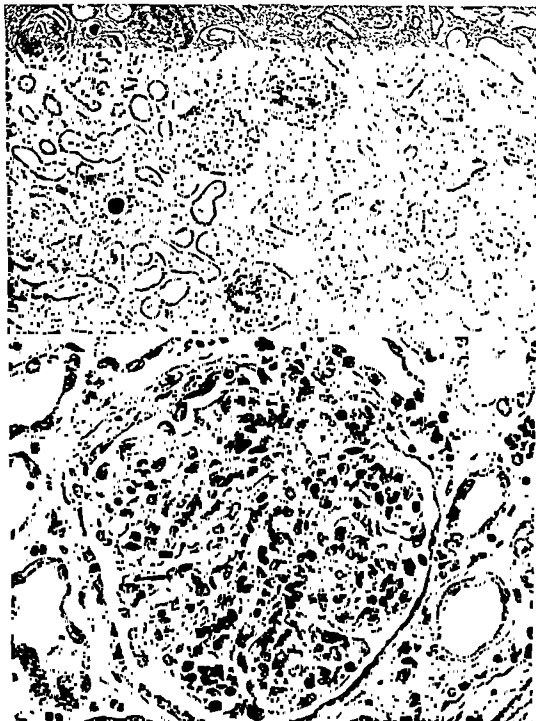


FIG A *Subacute diffuse glomerulonephritis* showing crescents, proliferative glomerulitis, focal interstitial inflammation with fibrosis, and exudate in tubular lumens

FIG B *Early crescent formation* in subacute diffuse glomerulonephritis showing proliferative glomerulitis The focus of early crescent formation is characterized by fibrinoid swelling of Bowman's capsule and swelling and proliferation of the epithelial cells Interstitial edema is also seen




Fig A *Red blood cells and casts* in distal tubules in a case of subacute diffuse glomerulonephritis

Fig C *Crescent* of subacute glomerulonephritis made up of proliferating epithelial cells some of which have become elongated to form fibroblasts

Fig B *Fibrin and proteid fluid* form a basis for a milieu in which proliferating cells may form a crescent

Fig D *Crescent* of epithelial cells in the proteid fluid in Bowman's space

Fig E *Fibrinoid degeneration* of interlobular artery in subacute diffuse glomerulonephritis.

generally to be taught that, by definition, the microscopic representation of subacute diffuse glomerulonephritis consists of glomerular crescents The three types include (1) the crescentic form (so-called extracapillary glomerulonephritis), (2) the proliferative form (so-called intracapillary glomerulonephritis, in which no crescents are present) and (3) the membranous form.

*Crescentic type*

The crescents of subacute diffuse glomerulonephritis occupy more or less of a segment of Bowman's space and are bounded by Bowman's capsule on the convexity (plates 61–63). The concave surface may be free in Bowman's space or may be fused with the periphery of the glomerular capillaries. They are generally considered to be of two types: the *epithelial* and the *fibrous*; actually they are probably of the same genesis, differing only in degree of development Epithelial cells, either from the visceral or parietal layers of Bowman's capsule, or from both layers, proliferate within a proteid fluid circulated in Bowman's spaces. The impression is gained that these epithelial cells, in such a medium become spindled and tapered so as to be morphologically and apparently functionally indistinguishable from fibroblasts White blood cells, including migrating monocytes, may contribute to the crescent and its organization The thought of epithelial cells transforming into fibroblasts may be unacceptable to those who adhere inflexibly to the absolute specificity of germ layers, but there is an increasing bulk of evidence supporting the thesis that the rigid specificity of germ layers is violated under certain conditions For example, the formation of cartilage in which epithelium plays the role of chondrocytes is a commonly observed experience in the so-called mixed tumors of salivary, lacrimal, sweat and mammary glands (Allen)

The end result of the crescent is a fibrous demilune either separated from the malpighian tuft or imperceptibly incorporated within it The degree of fibrosis of the crescent is usually similar to that of the tuft, but may be more or less advanced (plate 63) At times, the crescent is honeycombed into a so-called adenomatoid formation (plate 63 C) The fibrotic crescent is indicative of a long-standing process such as occurs uniformly in chronic glomerulonephritis. However, crescents, recent or old, are not specific for glomerulonephritis, inasmuch as identical formations may occur particularly in glomeruli in cases of arteriolar, especially malignant, nephrosclerosis, as well as in chronic pyelonephritis, apparently in response to ischemia due to arteriolar narrowing (plate 218 A) In the latter conditions, however, the crescents are confined to a few isolated glomeruli, whereas in subacute glomerulonephritis, they are more or less diffuse.

As a rule the malpighian tuft itself shows the lesion of proliferative or membranous glomerulonephritis In other words, there is generally glomerular ischemia associated with endothelial cell hyperplasia and thickening of the basement membrane. As a result of the glomerular ischemia, there are varying degrees of tubular atrophy, interstitial fibrosis and focal interstitial inflammation The extraglomerular vessels are usually spared but occasionally the afferent arterioles, particularly, are thickened It should be noted finally that while widespread glomerular crescents are generally indicative of a process of subacute duration, there are instances of acute glomerulonephritis in which crescents appear to have been formed within three weeks (plate 64)

## Chronic Glomerulonephritis

### *Clinical Picture*

The clinical picture of chronic glomerulonephritis is dependent upon and is therefore naturally as variegated as the histologic features of the nephritic kidney Any one sign or symptom, or combination of them, may characterize an individual case It is a remarkable fact that not infrequently the kidneys may be severely damaged before the patient or even the physician is aware of the disease. Proteinuria or hypertension may be the initial unsuspected finding of chronic glomerulonephritis in an apparently healthy person undergoing a routine physical examination. The true onset of the nephritis, if it was ever apparent, will very often have been forgotten, overlooked or misinterpreted and the patient will present himself in the late stages with easily correlated symp-

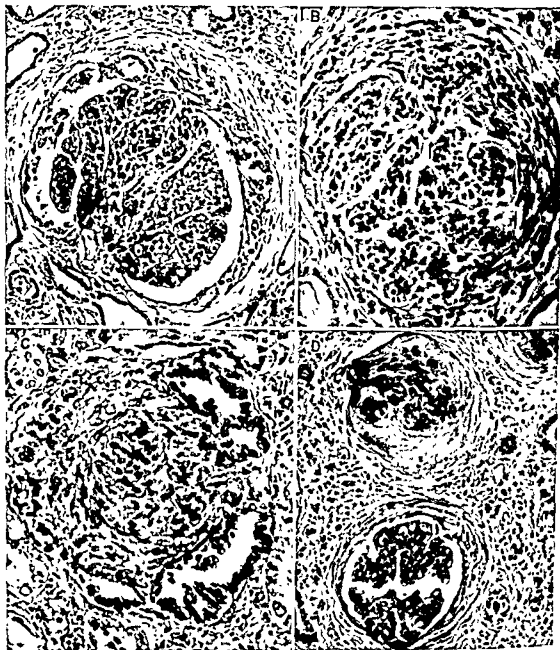



FIG A *Crescent of subacute diffuse glomerulonephritis* made up of proliferated epithelial cells The remainder of the malpighian tuft shows the picture of proliferative and early lobular glomerulitis

FIG B *Crescent in more advanced stage* than that shown in figure A The epithelial cells have elongated, become fibroblastic and the matrix has become collagenized

FIG C *"Adenoid formation"* in crescent of chronic glomerulonephritis

FIG D *Advanced stage of crescents* of chronic glomerulonephritis with partial encroachment onto tufts

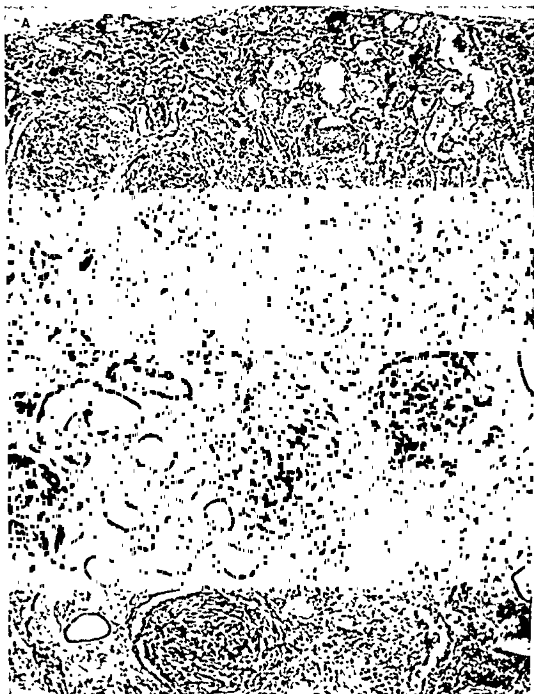



FIG. A *Subacute necrotizing glomerulonephritis* The glomerular changes appear fulminant consisting of polymorphonuclear leukocytic inflammation necrosis and disorganization of loops The tubular atrophy and interstitial fibrosis, over and above the acute changes, show the process to be older than indicated by the glomeruli However, the clinical history of the illness in this 20 year old male was only of three weeks' duration (A F I P Acc 111849)

FIG. B *Subacute glomerulonephritis of the exudative and proliferative type* The glomerular and interstitial fibrosis indicate that the acute inflammation is an exacerbation or prolongation of a glomerulonephritis of subacute duration



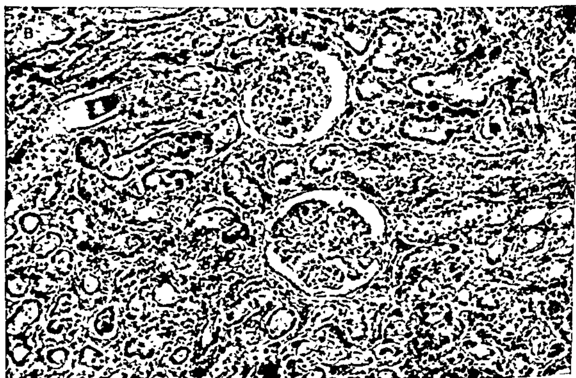




FIG A "*Large pale (white) kidney" of subacute diffuse glomerulonephritis* This swollen, nongranular kidney is the type associated with the clinical nephrotic syndrome

toms of edema, nocturia or polyuria. At times, however, the presenting symptoms may be more covert and may consist of anorexia, headache, vertigo, dyspnea, impairment of vision, epistaxis, or gastrointestinal symptoms. Indeed, in some instances, uremia itself may actually initiate the clinical syndrome in the form of headache, vomiting and mental confusion. It might be well to consider some of the individual signs and symptoms separately.

*Proteinuria*

Proteinuria is a long known and almost constant feature of chronic glomerulonephritis just as it is in the acute disease. When the albuminuria is abundant and protracted, it is followed by the clinical elements of the nephrotic syndrome: hypoproteinemia, reversal of the albumin-globulin ratio in the blood, hypercholesterolemia, and edema. In many cases, the degree of albuminuria decreases, therewith, the hypoproteinemia and edema clear. This occurrence is not a good omen, but, on the contrary, indicates a conversion of the large pale kidneys of lobular or membranous glomerulonephritis into the sclerotic, contracted kidneys. The progressive scarring of the glomeruli (rather than tubules) of these contracting kidneys reduces the leakage of protein.

*Edema*

Edema of renal origin is closely linked with the loss of albumin and the resulting hypoproteinemia. Consequently, the edema is usually most marked in the early months or years of the disease and tends to disappear with the diminution in the degree of albuminuria. The albuminuria, as mentioned, lessens with progressive contraction of the kidney. In other words, the presence of appreciable edema in patients with contracted kidneys is generally of cardiac rather than renal origin. There is totally inadequate evidence for believing that edema in glomerulonephritis is caused by diffuse capillary damage throughout the body (i.e., so-called "nephritic edema"). There is no histologic evidence of such damage. Moreover, on the basis of more recent analyses there is no longer reason to believe, as was formerly thought, that fluid of "nephritic" edema (as opposed to nephrotic or cardiac edema) contains a higher concentration of protein indicative of capillary damage. As previously indicated, Warren and Stead found the average concentration of protein to be 0.4 to 0.8 per cent in the edema fluid of patients with acute glomerulonephritis, this concentration is not significantly different from that in edema fluid of congestive heart failure.

*Hypertension*

Hypertension has become so closely identified with glomerulonephritis that its absence in cases with the nephrotic syndrome has encouraged the point of view that such cases represent a basically different disease from glomerulonephritis. Actually, many patients with "lipoid nephrosis" do eventually develop hypertension, particularly as the glomerular changes—including glomerular ischemia or at least narrowing of the glomerular capillaries—progress. In children and young adults especially, it may be necessary to take daily readings of blood pressure to detect evanescent rises of both the systolic and diastolic pressures to the vicinity of 140/90. Especially in cachetic patients, hypertension may be absent or minimal, in some cases of associated myocardial insufficiency, a drop in a pre-existing high blood pressure may occur. Remissions of hypertension are likely to take place in the intervals between the exacerbations or recurrent attacks.

As a rule, the level of blood pressure in chronic glomerulonephritis is lower than that of essential hypertension and not as labile. However, striking exceptions occur. *Malignant hypertension* of severe degrees (e.g., 250/150) may be superimposed onto chronic glomerulonephritis just as it may complicate other renal diseases such as chronic pyelonephritis, or benign nephrosclerosis. Histologically, these cases of chronic glomerulonephritis show the typical vascular lesions of malignant nephrosclerosis in addition to the lesions of glomerulonephritis. The clinical differentiation of chronic glomerulonephritis from essential hypertension may be difficult or impossible to make, especially in the middle-aged patients. The hypertension in chronic glomerulonephritis may cause severe headaches from hypertensive encepha-

# PLATE 66. Subacute Necrotizing Glomerulonephritis ("Lipoid Nephrosis")

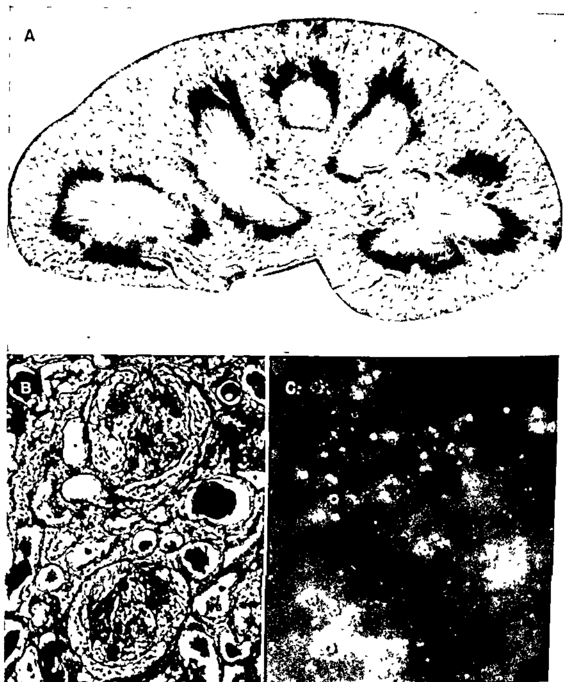
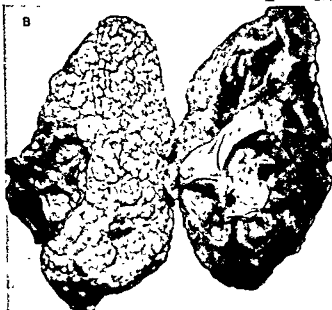


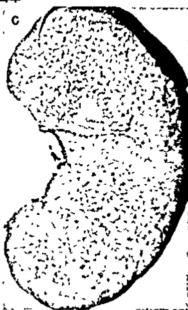

Fig A *Typically swollen pale kidney of subacute nephrotic glomerulonephritis*

Fig B *Gnarled glomeruli* from kidney illustrated in figure A Patient had clinical nephrotic syndrome plus hypertension Note the glomerular protein exudation and the tubular casts This glomerular picture is distinctly unusual with the nephrotic syndrome (Mallory-Heidhenhain stain )

Fig C *Doubly refractile maltese crosses* of cholesterol esters in epithelium of proximal convoluted tubules from kidney illustrated in figures A and B




FIGS. A, B AND C. *Chronic sclerosing glomerulonephritis*, the secondary contracted pale kidney with large, somewhat pale and irregular granulations (figures A, B, and C) in contrast with the redder, more irregular and finer granulations of benign nephrosclerosis and with the coarse scarring of the contracted kidneys of chronic pyelonephritis and that of multiple infarcts (plate 68A)

lopathy just as in essential hypertension, and on occasion may lead to death from cerebral hemorrhage or cardiac insufficiency. More commonly, the effect of the hypertension is cardiac hypertrophy, designed, so to speak, to compensate for the progressive destruction of the renal parenchyma. Eventually even the high level of the blood pressure is too low and the myocardium too weak to maintain adequate renal blood flow and clearance, as well as enough of a polyuria through the severely scarred kidneys, and death occurs from renal insufficiency.

*Retinopathy*

Hypertensive or arteriosclerotic retinopathy is present in almost every case of chronic sclerosing glomerulonephritis (Cannady and O'Hare) and is as ominous a prognostic sign as *it is in other types of hypertensive diseases* It usually portends death within one to two years. Failing of vision, rarely almost blindness and scotoma for certain colors, especially blue, occurs with the retinopathy. Retinal detachment which is often bilateral, is a particularly serious complication of hypertensive retinopathy in chronic glomerulonephritis as well as in malignant hypertension in general, although the detachment may correct itself if it occurs in association with toxemias of pregnancy. The retinopathy is correlated with the level of hypertension rather than the degree or type of renal impairment (plate 211 C–G).

*Exophthalmus is observed occasionally in* cases of chronic glomerulonephritis and is presumed to be related to the hypertensive encephalopathy

*Renal impairment*

One of the bewildering features of chronic glomerulonephritis is the variable tempo of renal deterioration not only from case to case but in individual cases The range of time from the initial insult to the final decompensation may be from months in some instances to decades in others.

Latent extrarenal infections, anamnestic renal reactions, the possible additional load of certain elements in the diet, and the unaccountable progression of fibrosis in different parts of the nephron are all factors which vary enormously in their influence on renal morphology and function How to control such relentless influence is the great problem in nephritis.

*Urine*

The proteinuria in chronic glomerulonephritis is almost constantly accompanied by a variety of casts including hyaline, granular, epithelial and fatty casts. There is a fairly close relationship between the albuminuria and the casts *As the albuminuria diminishes with contraction* of the kidney, the numbers of casts become less until only an occasional hyaline cast is present However, in the terminal stages, the large "renal failure" casts of Addis are commonly seen (plate 71). In those cases of abundant albuminuria associated with the nephrotic *syndrome, birefringent lipids—either free or in* epithelial cells—are found in the sediment (plate 73). These lipids are present in the urinary sediment of other cases with the nephrotic syndrome including amyloidosis, diabetic glomerulosclerosis and syphilitic nephrosis.

*Hematuria of slight degree is usually present* in cases of chronic glomerulonephritis in the contracted stage. Little or no hematuria is observed in patients with the large pale kidneys of chronic membranous or lobular glomerulonephritis. If abundant hematuria is present in chronic glomerulonephritis, an acute exacerba*tion or a complicating malignant nephrosclero*sis should be suspected. The relatively greater hematuria is a pinch of evidence in favor of the diagnosis of chronic glomerulonephritis as against amyloidotic nephrosis or diabetic glomerulosclerosis

*Specific gravity*

Often renal impairment may be compensated for many years by the capacity of the body to produce excessive amounts of urine. The polyuria *of the order of 2 to 3 liters tends to yield* an isotonic urine of a specific gravity of 1 010 (isosthenuric), or slightly less (hyposthenuric) with very little range. At the same time, the inability to concentrate the urine is somewhat neutralized by the release of sufficiently large

A



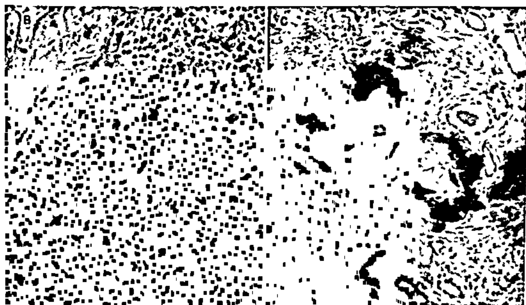
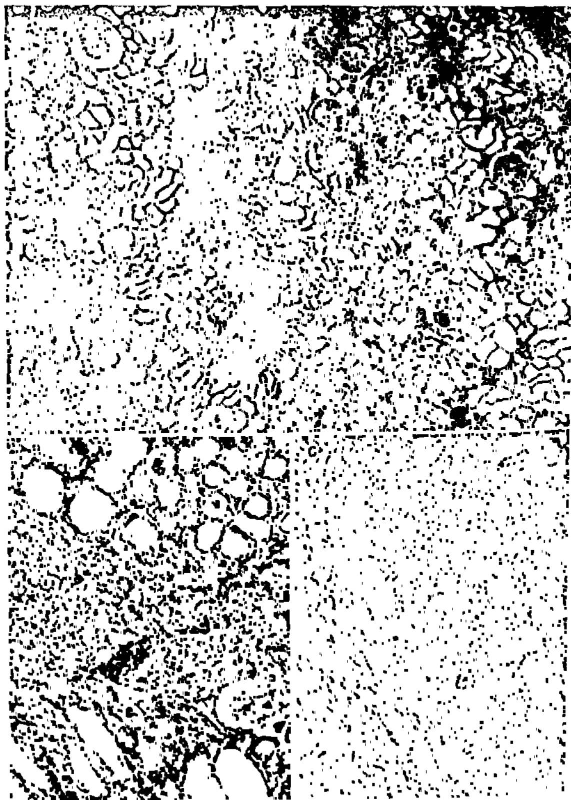



FIG A *Chronic sclerosing glomerulonephritis* in the contracted stage in contrast to the normal kidney below

FIG B *Secondary parathyroid hyperplasia* in chronic sclerosing glomerulonephritis with renal insufficiency

FIG C *Chronic sclerosing glomerulonephritis with metastatic calcification* in association with secondary parathyroid hyperplasia

PLATE 69. CHRONIC SCLEROSING GLOMERULONEPHRITIS



(Legends on facing page.)

quantities of glomerular filtrate With polyuria there is associated nocturia and polydipsia although the patient may nevertheless appear dehydrated In this compensated stage of renal impairment there is no azotemia, but when the polyuria is reduced, as from an accompanying myocardial failure, renal insufficiency with azotemia develops and uremia appears shortly The reduction of urinary output in this last phase of the disease is not characterized by an elevation of the specific gravity as in the oliguria of normal kidneys The tubules still do not possess an ability to concentrate the urine so that the specific gravity persists at about the level of 1 010 Such impairment of concentrating capacity is unusual in acute glomerulonephritis because destruction or dysfunction of the tubules only exceptionally is so marked in this early stage.

*Blood*

Anemia, of the secondary or normochromic type, is generally given much weight in the differentiation of chronic glomerulonephritis from other diseases The anemia may be profound and may reach counts of less than 2,000,000 red cells per cu mm Occasionally, a picture simulating pernicious anemia occurs in association with chronic glomerulonephritis, and Townsend and his associates have found evidence also of diminished gastric acidity The relationship to pernicious anemia is undoubtedly coincidental At the same time, the mechanism of the anemia still needs to be explained There is a positive correlation between the degree of renal impairment and the anemia (Townsend) The marrow is normal or hyperplastic, not megaloblastic The platelet count is not remarkable The current thought on the mechanism is that probably several factors are concerned (1) blood destruction, (2) blood loss in the urine, and (3) diminished blood formation as a result of some toxic influence on the marrow (Emerson).

*Osteodystrophy*

The changes in bones and parathyroid glands are described in the sections on hyperparathyroidism and renal rickets

## Chronic Sclerosing Glomerulonephritis

### *Pathology Gross Appearance*

As some of the inflamed glomeruli and their appertaining tubules become atrophic and fibrotic while others become hypertrophied, the soft smooth white kidney develops pits and fine yellowish-grey protruding nodules on its capsular surface (plates 67, 68 A) These changes constitute the grossly visible granules which are distributed rather uniformly over the capsular surface The crest of the granule corresponds to the hypertrophied dilated tubules, and the intervening depressed troughs to the atrophic nephrons The overlying capsule becomes thickened and may become adherent particularly to the depressed scarred areas so that when the capsule is removed some of the cortex may be torn away Occasionally small cortical glomerular and tubular cysts are present

The contraction may be so extreme that the kidney may weigh from 30 to 50 Gm and may have to be differentiated from a hypoplastic kidney Occasionally, however, the nephritic kidney, even though scarred, may in fact weigh much more than the normal because of the extent of the compensatory hypertrophy of nephrons The transformation from the "large white" to the secondary contracted "small pale" kidney may occur over a period of from two to five years, or many more, depending on such factors as the extent of initial renal involvement and the number and degree of the exacerbations

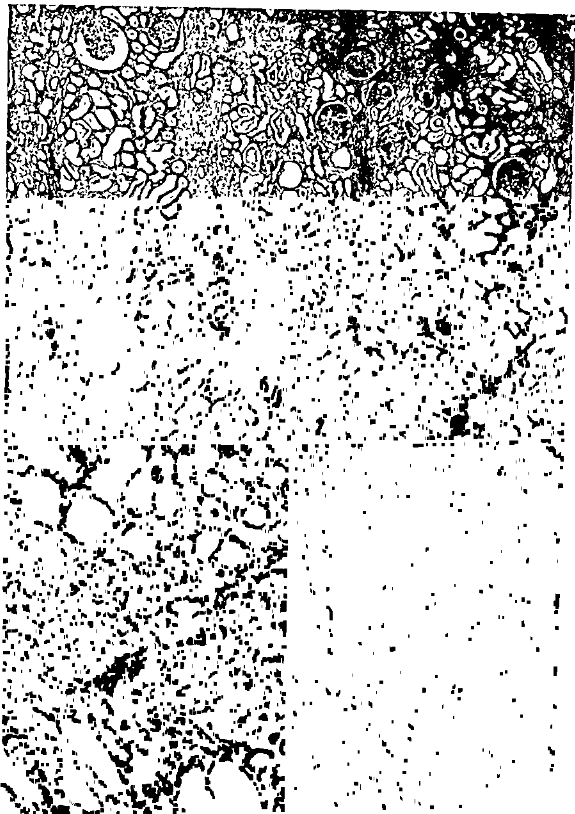
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Fig A *Low power view* of section of chronic sclerosing glomerulonephritis showing the atrophic nephrons adjacent to the dilated tubules of hyperplastic nephrons

Fig B *Interstitial fibrosis* of chronic sclerosing glomerulonephritis showing marked argyrophilia of the interstitial fibers (Wilder stain )

Fig C *Thickened adherent capsule* in chronic sclerosing glomerulonephritis showing contiguity between the argyrophilic fibers of the capsule and those of the atrophic renal parenchyma (Wilder stain )

PLATE 69. CHRONIC SCLEROSING GLOMERULONEPHRITIS



(Legends on facing page.)

quantities of glomerular filtrate. With polyuria there is associated nocturia and polydipsia although the patient may nevertheless appear dehydrated. In this compensated stage of renal impairment there is no azotemia, but when the polyuria is reduced, as from an accompanying myocardial failure, renal insufficiency with azotemia develops and uremia appears shortly. The reduction of urinary output in this last phase of the disease is not characterized by an elevation of the specific gravity as in the oliguria of normal kidneys. The tubules still do not possess an ability to concentrate the urine so that the specific gravity persists at about the level of 1.010. Such impairment of concentrating capacity is unusual in acute glomerulonephritis because destruction or dysfunction of the tubules only exceptionally is so marked in this early stage.

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The changes in bones and parathyroid glands are described in the sections on hyperparathyroidism and renal rickets.

## Chronic Sclerosing Glomerulonephritis

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The contraction may be so extreme that the kidney may weigh from 30 to 50 Gm. and may have to be differentiated from a hypoplastic kidney. Occasionally, however, the nephritic kidney, even though scarred, may in fact weigh much more than the normal because of the extent of the compensatory hypertrophy of nephrons. The transformation from the "large white" to the secondary contracted "small pale" kidney may occur over a period of from two to five years, or many more, depending on such factors as the extent of initial renal involvement and the number and degree of the exacerbations.

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Fig. B. *Interstitial fibrosis* of chronic sclerosing glomerulonephritis showing marked argyrophilia of the interstitial fibers. (Wilder stain.)

Fig. C. *Thickened adherent capsule* in chronic sclerosing glomerulonephritis showing contiguity between the argyrophilic fibers of the capsule and those of the atrophic renal parenchyma. (Wilder stain.)



FIG A *Chronic sclerosing glomerulonephritis* with fairly uniform and diffuse fibrous obliteration of lumens of glomerular capillaries, interstitial fibrosis and tubular dilatation and atrophy.

FIG B *Chronic sclerosing glomerulonephritis* showing various stages in the progression of the scarred glomeruli The hyperplastic dilated nephrons, in general, belong to the large, relatively salvaged glomeruli The "aglomerular nephrons" *constitute a possible debatable exception*




FIG A *Chronic sclerosing glomerulonephritis* with thin, apparently recent, proteid hyaline casts in distal convoluted tubules

FIGS B AND C *Dense hyaline casts* of chronic sclerosing glomerulonephritis Those of figure B especially simulate the proteid casts of the myeloma kidney but lack the giant cells

FIG D *Dense epithelial and granular renal failure casts* in collecting tubules of chronic sclerosing glomerulonephritis

PLATE 72. CHRONIC SCLEROSING GLOMERULONEPHRITIS IN HYPOPLASTIC KIDNEYS

A





B

(Legends on facing page.)

In cutting the kidney, the shrunken parenchyma offers considerable resistance to the knife The cortex is distinctly narrowed and so irregular that in places the medulla may extend practically to the capsule The normal markings are obscured and grey, fibrous streaks or yellowish fatty foci mottle the surface The arteries may be appreciably thickened and, indeed, in this advanced stage, the gross picture may be indistinguishable from that of the primary contracted "vascular" kidney As in most instances of renal atrophy, no matter the cause, the pelvic fat tends to be increased in proportion to the atrophy (plate 278 C)

The granularity of the surface of the kidney in chronic sclerosing glomerulonephritis tends to be a shade coarser, paler, and somewhat less uniform than the fine granularity of benign nephrosclerosis (plate 67, 209 A) The surface irregularity caused by chronic pyelonephritis, arteriosclerosis and multiple infarctions is considerably more marked (plates 186, 207, 260)

### *Pathology Histologic Appearance*

*Glomeruli*

Histologically few glomeruli are spared change The interval between glomeruli is necessarily diminished in the contracted kidney of chronic glomerulonephritis, but these distances tend to be fairly equal This situation also exists in benign nephrosclerosis but is in sharp contrast to the compact clusters of glomeruli in chronic pyelonephritis, or in infarcted areas Although few glomeruli remain normal in chronic sclerosing glomerulonephritis, there is a wide range in the degree of involvement of individual glomeruli Some may be reduced to a densely collagenized sphere in which the tuft has been tightly fused with the thickened Bowman's capsule and the whole glomerular unit reduced in size (plate 70 A), others show only partial eccentric fibrosis with varying degrees of adhesion of capillary loops to each other and to Bowman's capsule (plates 70 B, 71 A) The portions of such tufts that have escaped the obliterative fibrosis present in adjacent loops tend to be ischemic and to show some thickening of the basement membranes In general there is a parallel between the degree of fibrosis of the tuft and Bowman's capsule Commonly in this type of glomerulonephritis the few glomeruli that are not injured are larger in diameter, sometimes about twice the normal size, as if stimulated to compensatory hyperplasia

*Tubules*

If we accept the classical notions that the tubules are dependent on the integrity of the glomeruli for the predominant source of their blood supply, then in diffuse glomerulonephritis we should expect profound tubular damage. The fact is that the tubular damage varies considerably and it is by no means possible always to correlate the degree of tubular alteration with the amount of glomerular change Usually there is some tubular degeneration in association with glomerulonephritis which may take the form of fatty changes in the proximal convoluted tubules, epithelial desquamation, polymorphonuclear leukocytic infiltrations, casts and foci of frank necrosis Occasionally there is marked necrosis of tubular epithelium in great disparity with the glomerular change, at other times, there may be striking glomerular damage with little apparent alteration of the tubules It would seem therefore that other factors must play a role in the glomerulo-tubular relationship The evidence leads one to suspect that the dependence of the tubules on the glomerulus and its efferent arteriole, although usually great, is far from necessarily complete The amount of nourishment supplied to the tubules from the afferent arteriole

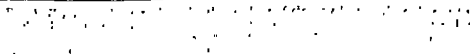
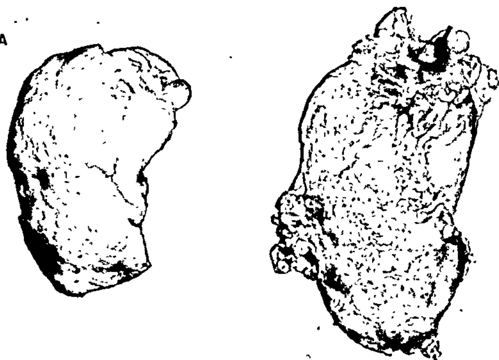


FIG B *Chronic sclerosing glomerulonephritis* Section taken from the kidneys illustrated above The fibrosis of the glomeruli and interstitium and the arterial and arteriolar sclerosis in this child's kidneys are indistinguishable from the corresponding changes in adults

PLATE 72 Chronic Sclerosing Glomerulonephritis in Hypoplastic Kidneys




(Legends on facing page )

In cutting the kidney, the shrunken parenchyma offers considerable resistance to the knife The cortex is distinctly narrowed and so irregular that in places the medulla may extend practically to the capsule The normal markings are obscured and grey, fibrous streaks or yellowish fatty foci mottle the surface The arteries may be appreciably thickened and, indeed, in this advanced stage, the gross picture may be indistinguishable from that of the primary contracted "vascular" kidney As in most instances of renal atrophy, no matter the cause, the pelvic fat tends to be increased in proportion to the atrophy (plate 278 C)

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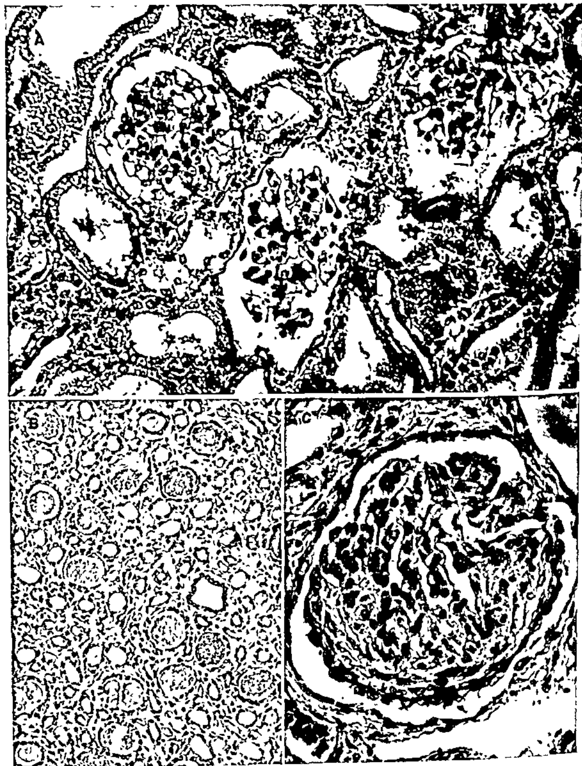
*Tubules*

If we accept the classical notions that the tubules are dependent on the integrity of the glomeruli for the predominant source of their blood supply, then in diffuse glomerulonephritis we should expect profound tubular damage. The fact is that the tubular damage varies considerably and it is by no means possible always to correlate the degree of tubular alteration with the amount of glomerular change Usually there is some tubular degeneration in association with glomerulonephritis which may take the form of fatty changes in the proximal convoluted tubules, epithelial desquamation, polymorphonuclear leukocytic infiltrations, casts and foci of frank necrosis Occasionally there is marked necrosis of tubular epithelium in great disparity with the glomerular change, at other times, there may be striking glomerular damage with little apparent alteration of the tubules It would seem therefore that other factors must play a role in the glomerulo-tubular relationship The evidence leads one to suspect that the dependence of the tubules on the glomerulus and its efferent arteriole, although usually great, is far from necessarily complete The amount of nourishment supplied to the tubules from the afferent arteriole

Fig A *Hypoplastic kidneys which also show evidence of chronic sclerosing glomerulonephritis* Anomalous kidneys are, in general, more vulnerable to inflammation than normal kidneys The possibility cannot be excluded that these kidneys were of normal size at birth and that the glomerulonephritis and contraction occurred early in childhood

Fig B *Chronic sclerosing glomerulonephritis* Section taken from the kidneys illustrated above The fibrosis of the glomeruli and interstitium and the arterial and arteriolar sclerosis in this child's kidneys are indistinguishable from the corresponding changes in adults

PLATE 73. Chronic Membranous Glomerulonephritis ("Lipoid Nephrosis")




(Legends on facing page.)

via Ludwig's vessel and from shunts off the interlobular and arcuate arteries may, under abnormal conditions, be considerable

Many of the nephrons, however, do undergo atrophy following the lead of the glomerulus. Such atrophic nephrons take the form of small tubules isolated in a contracted focus of fibrous tissue which, grossly, constitutes the depressed areas between the granules (plate 69) The tubules of the intervening nephrons are inclined to undergo hyperplasia, hypertrophy and often dilatation, a process ascribed teleologically to compensation These hypertrophied tubules usually, but not necessarily, associated with a relatively intact or hypertrophied glomerulus, make up the crest of the granules observed on the surface of the kidney

*Interstitium*

As stated, in the acute phase of glomerulonephritis the interstitium may be edematous and focally infiltrated with polymorphonuclear leukocytes, lymphocytes and plasma cells In later stages, the edematous stroma is replaced by firm, generally well vascularized stroma which contains abundant reticulin fibers The preponderance of the interstitial fibrosis was responsible for the the former application of the term "chronic interstitial nephritis" in many instances of chronic glomerulonephritis, but it now seems clear that the interstitial scarring is quite secondary to the glomerulonephritis Foci of cellular infiltration form a constant part of the picture, the cells consisting principally of lymphocytes, histiocytes and plasma cells. Occasionally deposits of doubly refractile lipids are found in the stroma just as they are in the tubular epithelium, especially in chronic membranous or lobular glomerulonephritis (plate 76)

*Vascular changes*

As the glomerulonephritis progresses there is greater likelihood of the development of one or more varieties of vascular change Although in the acute stage of glomerulonephritis there may be no evidence of extraglomerular vascular disease, it is important to emphasize that in the later stages the degree and type of vascular involvement may so closely simulate the changes in the primarily vascular kidney as to make differentiation impossible on the basis of examination of the vessels alone The changes may take one of the following forms: (1) endarteritis obliterans, (2) arteriolosclerosis or (3) arteriolar necrosis

1 *Endarteritis obliterans* is represented simply by a sclerotic intimal thickening of arteries It is the same process that results in the physiologic obliteration of the ductus arteriosus, for example In chronic glomerulonephritis arteries of all sizes may be involved just as in the nonhypertensive "senile kidney" The elastic laminae are usually not reduplicated as in hyperplastic sclerosis although fine elastic fibrils may be scattered through the outer part of the intima The intima may show fatty and hyaline thickening The pathogenesis of this intimal change is not clear but it appears not to be related to hypertension Histologically this form of endarteritis is quite like that found in association with nonspecific chronic inflammation as, for example, at the base of a gastric ulcer Fishberg prefers to regard the arterial change as a consequence of obstruction to the flow of blood due to the obliterated glomerular capillaries

2 *Arteriolosclerosis* is practically a constant feature of chronic glomerulonephritis in which there has been hypertension of some years'

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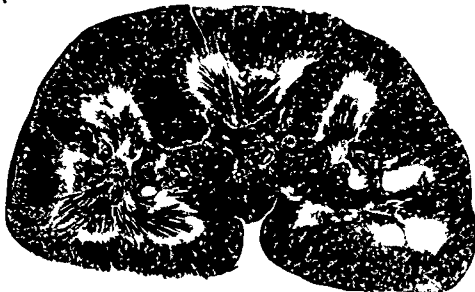
FIG A *Chronic membranous glomerulonephritis (lipoid nephrosis)* of an infant aged 3 years, showing glomeruli that might perhaps be called normal but which in fact show increased cellularity, a delicate thickening of basement membranes and protein precipitate in Bowman's spaces Fat is present in the tubules The illness was of four months duration and followed an episode of whooping cough (AFIP Acc 39521)

FIG B *Protein casts* in collecting tubules from kidney of "lipoid nephrosis" illustrated in figure A

FIG C *Unequivocal, unresolved glomerulitis* from same case as illustrated in figure A, furnishing clue to the over-all glomerulopathic nature of "lipoid nephrosis"

## PLATE 74 Chronic Membranous (Nephrotic) Glomerulonephritis ("Lipoid Nephrosis")

A



B

Fig A *Chronic membranous glomerulonephritis* showing the swollen (yellow) cortex associated with the clinical nephrotic syndrome in an adult

Fig B *Membranous (and proliferative) glomerulitis* from kidney illustrated in figure A Patient had the clinical nephrotic syndrome in conjunction with hypertension Note fat vacuoles in prox-

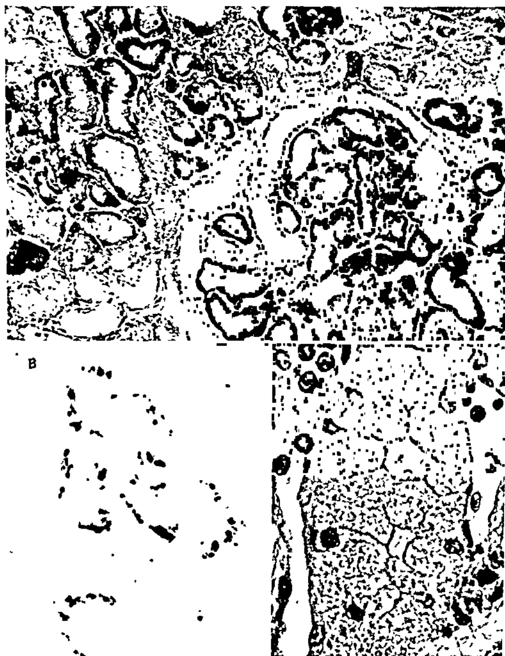



FIG A *Abundant fat* is present in the epithelium of the proximal convoluted tubules in this case of chronic membranous glomerulonephritis (Sudan III stain)

FIG B *Doubly refractile fat* in the epithelium of proximal convoluted tubules is observed with polarized light

FIG C *Hyaline acidophilic granules* are prominent in the epithelium of the proximal convoluted tubules The assumption that the granules represent reabsorbed protein warrants re-examination, the granules more likely are the result of swollen intrinsic cytoplasmic constituents

ment membranes of the glomerular capillaries (*plates 74 B, 78*). Their walls are so rigid as to resemble bent wire even more closely than the glomerular "wire-loops" of disseminated lupus erythematosus (plate 79) However, the lesions of the latter are focal within any given tuft and are more brightly acidophilic than those of membranous glomerulonephritis In addition, the increased thickness of the walls of the glomerular capillaries in membranous glomerulonephritis is rarely as great as it is in lupus erythematosus in which the walls often bulge in a verruciform fashion Finally, the focal lupus lesion is often associated with an exudative glomerulitis in the remainder of the tuft, a feature not part of the picture of membranous glomerulonephritis

Frequently in membranous glomerulonephritis, there are slight to moderate degenerative and regenerative changes of the tubular epithelium, particularly of the proximal convoluted tubules. Mild focal atrophy of the tubules with replacement fibrosis is common Lipid, partially birefringent, is often present in the epithelium of the proximal tubules. Proteid casts are common and a few casts of hemoglobin may also be present in the distal nephron. Inflammatory cells are sparse, but scattered foci of lymphocytes in the interstitium may occur Usually no significant extraglomerular vascular changes are observed, except in the presence of protracted hypertension

The changes just described are found in the straightforward cases of chronic membranous glomerulonephritis. However, the strikingly uniform glomerular changes may be altered by inflammation and distortion of the glomerular capillaries Frequently, residual evidence of an antecedent membranous glomerulonephritis can be detected among the only partially scarred glomeruli of contracted kidneys This is what usually happens in those patients whose clinical picture of the nephrotic syndrome is transformed into that of chronic sclerosing glomerulonephritis As the glomeruli become progressively scarred, the large smooth, pale kidney shrinks and develops a granular surface While this is happening, the albuminuria lessens, the edema tends to clear and renal insufficiency begins to appear

*Chronic lobular glomerulonephritis.* In lobular glomerulonephritis, as in the membranous form, the lesion is diffuse, sparing no glomerulus (plate 80). The glomerular tufts are sharply lobulated into from four to eight hyalinized spheres of rather uniform size There is some tendency for the periphery of each lobule to be laminated by two or three layers of endothelial cells although here and there a lobule is made up of a mass of cells (presumably mostly endothelial) with minimal stroma Occasionally, the thickened capillaries rimming the spheres are dilated as in diabetic glomerulosclerosis with which, incidentally, this lesion is commonly confused (plate 245).

The lobulation is sometimes referred to as lobular "simplification" of glomerular structure. This "simplification" is a superficial impression that is not supported by the facts of finer histologic study. For example, with routine hematoxylin-eosin stain, the lobules appear to represent merely hyaline thickening of "intercapillary" tissue. When stained with silver (for example, the modified Bielschowsky stain) it is of some surprise to note that the acidophilic spheres are, in reality, made up of small curlycues of argyrophilic fibers, rather than a mass of intercapillary tissue These fibers represent the walls of the glomerular capillaries distorted by irregular thickenings and proliferations, often in association with hyperplastic endothelial cells. There is no impressive reason to continue to believe that this material is simply a broadening of intercapillary tissue. The same problem arises in connection with the lesion of diabetic glomerulosclerosis, and is treated in more detail in the discussion of this lesion It is clear that many who regarded the matter as settled a few years ago are now reconsidering the question of the role, or even existence of intercapillary tissue in these lesions. To reemphasize the point, in the case of lobular glomerulonephritis, as in diabetic glomerulosclerosis, as well as in amyloidosis of the glomeruli, the evidence indicates that the *walls* of the glomerular capillaries rather than the intercapillary tissue participate in the genesis of the lesions.

The tubular, interstitial and vascular changes




FIG A *Lipid filled histiocytes* embolic to glomerulus in a case of death due to blast injury

FIG B *Glomerular fat embolism* following multiple bone fractures

are similar to those of membranous glomerulonephritis

### Relationship of Membranous and Lobular Glomerulonephritis to "Lipoid Nephrosis"

There are three principal varieties of widespread glomerular lesions characterized by hyaline lobulation of the malpighian tuft, these are amyloidosis, diabetic glomerulosclerosis and lobular glomerulonephritis (plate 245). It is of interest to note that each of these lesions, when widespread, is associated with the nephrotic syndrome The pivotal feature of the nephrotic syndrome is the loss of protein, principally albumin, in the urine The proteinuria is best attributed to the increased permeability of the glomerular capillaries In the lobular tufts of these three lesions, the histologic evidence indicates that such increased permeability of the capillaries occurs as a result of their dilatation, their obviously altered basement membrane about the spheres, or the operation of both factors In membranous glomerulonephritis, the basis for the proteinuria is the diffuse alteration of basement membranes which spares none of the glomerular capillaries.

Although the clinical features of "lipoid nephrosis" may be fully developed in diabetic glomerulosclerosis, and in renal amyloidosis, the specific features—both pathologic and clinical—of these two entities, permit their ultimate segregation from the category of "lipoid nephrosis" There remain, therefore, as the histologic counterpart of "lipoid nephrosis," two clearly definable forms of glomerulonephritis: (1) chronic membranous glomerulonephritis, and (2) chronic lobular glomerulonephritis In the past, despite the efforts of Bell and others, the glomerulonephritic nature of "lipoid nephrosis" has been umbraged by emphasis on the possible presence of abnormal proteins with excessive permeability, on the overproduction of antidiuretic hormone, and on the presumed impairment of the capacity of the renal tubules to handle protein However, none of these explanations has ever been shown to account adequately for the physiologic derangements of the symptom-complex known as the nephrotic syndrome The following summary of the glomerulonephritic concept of "lipoid nephrosis" seems in keeping with the bulk of evidence:

1 That "lipoid nephrosis" is the clinical set of signs and symptoms outlined above which occurs as a part of the picture of chronic glomerulonephritis; that it corresponds to the "degenerative stage" in Addis' terminology of glomerulonephritis; and that "pure" or "mixed" types of lipoid nephrosis represent degrees of glomerular alteration rather than intrinsically different diseases

2. That *"lipoid nephrosis" is in reality* a definite variety of subacute or chronic (membranous or lobular) glomerulonephritis with specific histologic alterations of the glomeruli, which are less obvious in children than in adults. This diminished histologic glomerular reactivity may be said to be more or less characteristic of the glomeruli of children as opposed to those of adults.

3. That it is possible to interpolate, merely from a histologic examination of the sections of the kidneys, that the patients had had the nephrotic syndrome

4 That the clinical syndrome centers about the loss of abundant protein in the urine with consequent hypoproteinemia and edema and reversal of the albumin-globulin ratio The cause of the hypercholesterolemia is not clear, but the lipidemia is a concomitant of severe protracted albuminuria, whether the cause is glomerulonephritis, amyloidosis, or diabetic glomerulosclerosis.

5 That the much overemphasized difference between the "pure" (without hypertension, hematuria or renal insufficiency) and the "mixed" types is subordinate to the main issue, and is dependent on the relative degrees of ischemia and integrity of glomerular capillaries

6 That, despite the frequent absence of overt antecedent infection in chronic membranous glomerulonephritis, or lobular glomerulonephritis, there is sufficient evidence of transitional histologic similarity to the sclerosing types of glomerulonephritis to lead us to believe that their etiology is related.

7 That the nephrotic syndrome charac-

PLATE 78 CHRONIC MEMBRANOUS GLOMERULONEPHRITIS ("LIPOID NEPHROSIS"): THE "LARGE WHITE KIDNEY"

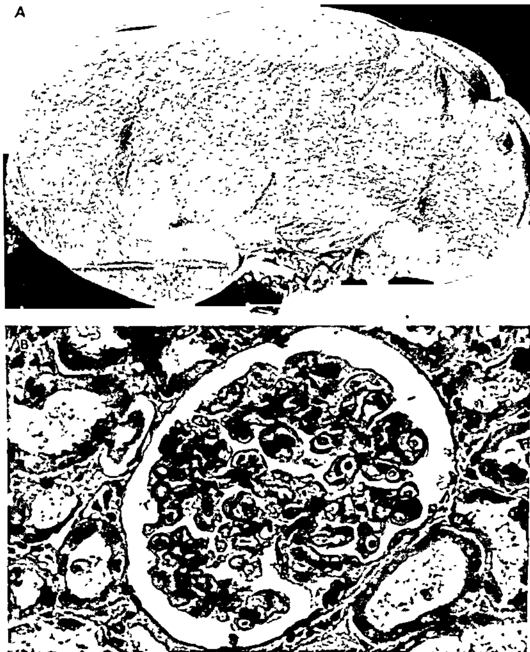



FIG A *The typical "large white kidney"* of chronic membranous glomerulonephritis ("lipoid nephrosis")

FIG B *Glomerulus from the "large white kidney"* of "lipoid nephrosis" illustrated in figure A This glomerulus, quite representative of the remainder in this kidney, shows diffuse thickening of the capillary basement membrane, chiefly responsible for the term *membranous glomerulonephritis* Such thick basement membranes are apparently astonishingly permeable to proteins

teristic of chronic membranous or chronic lobular glomerulonephritis may persist to the end or may become altered to approach the clinical picture of chronic sclerosing glomerulonephritis, in accordance with the tempo in which the glomeruli are converted into those of the sclerosing variety (contracted kidney)

8. *That, because of the uniform, universally distributed collagenous alteration of the glomerular capillaries in chronic membranous glomerulonephritis, it would be of particular interest to learn the effect of ACTH especially on this individual form of the glomerulonephritides*

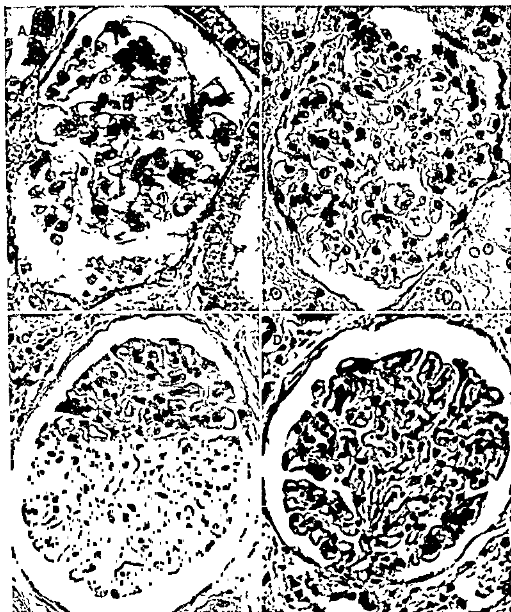
### Exacerbation of Chronic Glomerulonephritis

In many cases, exacerbations in chronic glomerulonephritis are known to be precipitated by overt infections Nevertheless, in a large number of cases, the process of acute diffuse glomerulonephritis continues through the subacute and chronic states in the absence of apparent infections The source of the momentum for the evolution of this series of changes is not altogether clear If, for example, the child's initial acute glomerulonephritis followed an illness of scarlet fever, can it be supposed that the same glomerulitic agent smoulders for years afterwards, and produces, finally, the changes we recognize as subacute or chronic glomerulonephritis? Or, can we presume that there is sufficient propulsion supplied by the initial glomerulitic reaction to carry the disease slowly through its subsequent stages? Neither of these concepts seems entirely adequate to explain the clinical and histologic observations of most cases, except, perhaps, in some instances of membranous and lobular glomerulonephritis ("lipoid nephrosis")

The fact is that there is histologic evidence of exacerbation of glomerulonephritis in the form of acute glomerulitis superimposed onto various stages of chronic glomerulonephritis It is likely that in many instances repeated nephropathic infections or reactions, such as respiratory infections or allergies, occur which are clinically undetected On the other hand, one must reckon with the possibility that, after the first attack, a diminished number of glomeruli are left to carry on the original burden of work. Under this condition, it is conceivable that the remaining glomeruli are more vulnerable to injury. Such injury may result, according to Addis, also from the excessive renal work imposed by a diet rich in proteins, a diet that would be innocuous to an individual with a normal number of glomeruli. By the same token, these handicapped kidneys may be particularly liable to other types of insults from infections that might spare normal kidneys

With regard to many cases of chronic membranous or lobular glomerulonephritis ("lipoid nephrosis"), however, it appears probable that the initial damage may be self-perpetuating without histologically evident exacerbations As already stated, the exaggerated permeability to proteins is the outstanding feature of the glomerular abnormality in these diseases; and it is plain, from a review of the bland, static-appearing, histologic picture of these entities—particularly of membranous glomerulonephritis—that essential maintenance of the histologic, and usually the physiologic, *status quo* responsible for the one sign (albuminuria) probably persists over most of the duration of the disease in many cases. As has been mentioned, however, at the time the clinical picture changes (that is, when the albuminuria and edema improve or even disappear) the process of glomerular sclerosis, tubular atrophy, and interstitial fibrosis begins, and the contraction of the large white kidney is initiated At this time, too, hypertension and progression of renal tubular dysfunction tend to replace the nephrotic syndrome. When all this occurs, the common infectious, allergenic, or anamnestic factors, leading to exacerbation of glomerulonephritis in general, in all likelihood have superimposed their effects on these membranous or lobular forms

Stated in other words, chronic membranous as well as chronic lobular glomerulonephritis may persist as such to the termination of the disease without histologic evidence of acute or progressive glomerular change In such instances, the clinical picture is very likely to be that of the so-called "pure" lipoid nephrosis. In other cases, to repeat, the membranous or lobular glomerulonephritis may, with exacer-




FIGS. A to D represent increasing degrees of thickening of glomerular capillary basement membrane. Figure A is characteristic of the infantile type; these glomeruli rarely seem to be able to respond after the fashion observed in adults as in figure D. Figures C and D, often mistaken for the "wire-loops" of lupus erythematosus, are pathognomonic of the clinical nephrotic syndrome by virtue of the diffuseness of the changes in the basement membranes which involve all the glomeruli.

bations, evolve into the contracted kidney of chronic sclerosing glomerulonephritis This is to say, again, that the type 2 of Ellis may become type 1, rarely does the reverse occur Similar renewal of glomerular insults occurs in all of the other forms of glomerulonephritis. The exacerbation takes the form of acute, exudative, proliferative, or necrotizing inflammation, not only of the previously spared glomeruli, but of those glomeruli that have already been altered (plate 81). Among the latter, those portions of the glomerular tuft that have not become fibrotic may show the acute changes in the capillary loops (plates 81, 82). Moreover, we have observed that the collagen of even scarred segments of glomeruli may show evidence of exacerbation in the form of acute fibrinoid degeneration (plate 82). It is an interesting fact, observed by many investigators, and especially emphasized by Seegal and Earle, that the latent period between the original infection and the development of acute glomerulonephritis is longer than that which precedes the subsequent infections and exacerbations The latent periods of the exacerbations may often be shortened to 24 hours, suggesting prior sensitization or anamnestic reaction. Again this feature contrasts with the usually equal intervals between infection and recrudescence of rheumatic fever, notwithstanding prior sensitization The reasons for these diverse immuno-allergic responses are not known.

## Focal Glomerulonephritis

Four forms of focal glomerulonephritis occur:

1 Focal nonsuppurative glomerulonephritis
2 Focal suppurative glomerulonephritis
3 Focal endocarditic glomerulonephritis
4 "Wire-loop" glomerulonephritis of disseminated lupus erythematosus

Although it may be entirely impossible always to distinguish some of these forms clinically, they are histologically and probably pathogenetically distinct

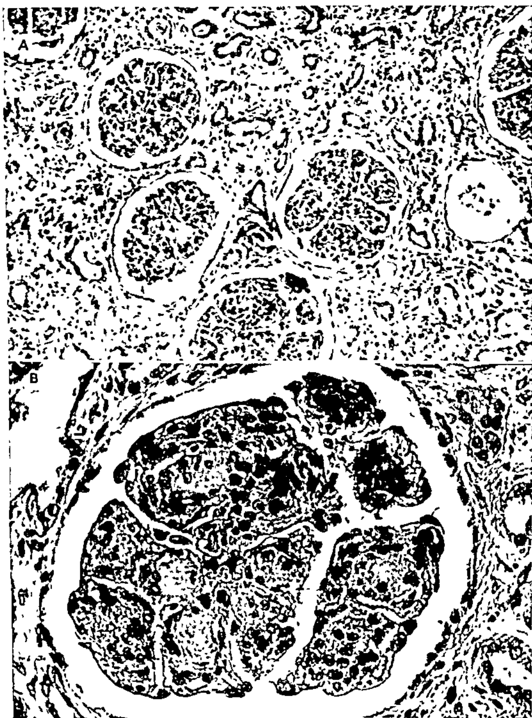
### *Nonsuppurative Focal Glomerulonephritis*

Acute nonsuppurative glomerulonephritis ["infektnephritis" (Munk) or "herdnephritis"] may complicate any of a great variety of infections, chemical poisonings (for example, mercuric chloride and arsenic) and allergic reactions to a number of drugs, particularly the sulfonamides (plate 139). The infectious diseases may be bacterial, viral, rickettsial and may be due even to fungi (plate 57 D) or treponemas (for example, relapsing fever), the presence of bacterial endocarditis is not necessary for its occurrence The clinical evidence of focal nephritis is generally minimal and consists of hematuria, albuminuria, and casts and leukocytes in the urinary sediment. For all clinical purposes, the lesions clear promptly if the primary disease is survived. Unlike many of the lesions of acute diffuse glomerulonephritis, the focal lesions occur at the height of the primary infection, rather than during the convalescence. This fact and the questionable assumption that bacteria are present locally have led to the conclusion (Fishberg) that focal lesions are due to the direct action of invading bacteria and other agents in contrast to the allergenic nature of diffuse glomerulonephritis This thesis is difficult to support on histologic grounds

The vast majority of lesions of acute focal nonsuppurative glomerulonephritis have the individual glomerular pattern of any of the forms of acute diffuse glomerulonephritis In

Fig A *Chronic lobular glomerulonephritis* of the type characterized by lobules of hyalinized glomerular capillaries The clinical picture is typically that of the nephrotic syndrome The lobules are much more diffuse and uniform in size than those of diabetic glomerulosclerosis This lobular picture may be combined with sclerosing glomerulitis, in which case the clinical picture is correspondingly altered

Fig B *Chronic lobular glomerulonephritis* from figure A The hyalinized lobules superficially simulating diabetic glomerulosclerosis consist of masses of capillaries generally with a dilated loop at the periphery of the lobule The silver stain reveals the entangled capillary masses in the lobules in contrast to the orderly lamination of silver fibers of diabetic glomerulosclerosis (compare plate 243)




(Legends on facing page.)

other words, the focal glomerular change may be proliferative, exudative, necrotizing, hemorrhagic or a combination of any of these (plates 83, 84) *No bacteria are found in the lesion*, contrary to the usual description of them. Nor are they necessarily or even commonly associated with excretion abscesses unless they are of the suppurative type (plate 84 B) In other words, these forms of acute focal glomerulitis are also regarded as a toxic or allergic response *to the products* of organisms or drugs. To deny, as some do, that *focal* allergic reactions occur in the kidney is to fail to give interpretive consideration not only to these lesions, but to others, such as those of lupus erythematosus focal endocarditic glomerulonephritis, acute focal vascular alterations and, of course, acute focal interstitial nephritis

The nondestructive nature of most of the lesions of acute focal nonsuppurative glomerulonephritis allows for complete architectural resolution. However, some glomeruli are so extensively altered that they are destined to be scarred It is therefore reasonable to assume that occasional scarred glomeruli in otherwise normal kidneys may represent the end result of acute focal glomerulonephritis appearing during a previous, perhaps forgotten disease. These obliterated glomeruli are manifestly of no clinical significance, but they may complicate the differential histologic diagnosis It is possible that some examples of the so-called "congenital glomerulosclerosis" represent the endstage of a similar process, in other instances, ischemic atrophy appears to account for these focal lesions of infancy.

### *Suppurative Focal Glomerulonephritis*

*Relatively infrequently*, there are found lesions of acute focal suppurative glomerulonephritis that are obviously produced by the direct action of the organisms themselves which have reached the glomeruli through the blood stream in sepses or as bacterial emboli (plate 84 B). In such glomeruli, as a rule, only *a portion* of the malpighian tuft is altered, quite as would be expected with focal inflammation due to pyogenic organisms The inflammatory response consists primarily of a clump of polymorphonuclear leukocytes with a degree of destructive change in the glomerular capillaries that happen to be included in the focus. Not only may bacteria be found in this *type of focal glomerulitis, but there may* be associated excretion abscesses in the corticomedullary junction. However, it is to be stressed that this picture is the *unusual* one of acute focal glomerulonephritis.

### *Focal Endocarditic Glomerulonephritis*

For reasons to be explained the term *focal endocarditic glomerulonephritis* is to be used here instead of *focal embolic glomerulonephritis* or multiple glomerular embolization. This lesion occurs in from 53 per cent (Bell) to 92 per cent (Baehr) of the kidneys in cases of subacute bacterial endocarditis (that is, endocarditis of more than six weeks duration). The incidence of the lesions in our own experience corresponds closely with that of Bell's as far as subacute bacterial endocarditis is concerned, but differs from his in that he has observed the lesion in 2.9 per cent of rheumatic endocarditis, in 7 1 per cent of acute primary bacterial endocarditis (less than six weeks duration) and in 5 8 per cent of secondary (focus of infection demonstrable) endocarditis We have seen only four cases of this lesion in which no endocarditis was present but which were associated instead with allergic arteritis Therefore we regard the lesion as strongly presumptive evidence of subacute bacterial *endocarditis* It is possible that in some instances the so-called acute bacterial endocarditis existed longer than the six weeks of evident symptoms It is also known that the lesion of bacterial endocarditis has been assumed to be absent when it is actually present but of practically microscopic *dimensions On the other hand*, in view of the concept to be mentioned of the nonembolic nature of the lesions, it becomes reasonable that, in isolated instances, the glomerulitic lesion may occur without endocarditis but with some corresponding immuno-allergic state. It is of interest that in the so-called "bacteria-free stage" of subacute bacterial endocarditis, the glomerular complication is much more likely to be an acute diffuse glomerulonephritis than a focal endocarditic glomerulonephritis, occasionally the two forms coexist.

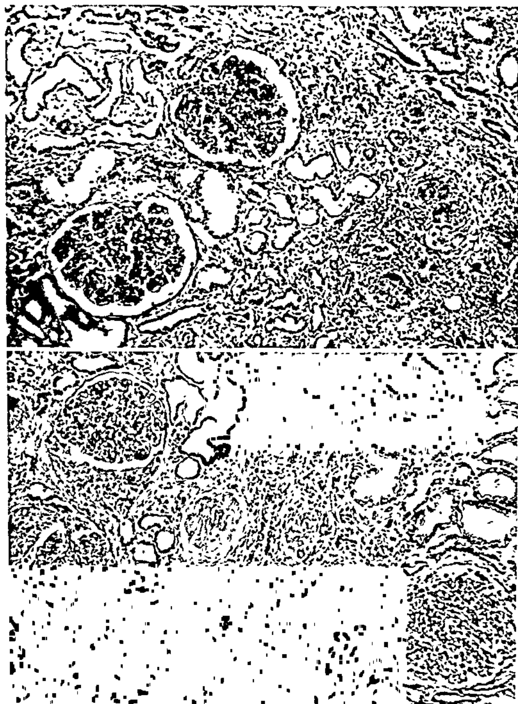



FIG A *Chronic sclerosing glomerulonephritis with acute exacerbation* as shown by the exudative glomerulitis in two large glomeruli on the left

FIG B *Chronic sclerosing glomerulonephritis with acute exacerbation* In two glomeruli, the acute inflammation is present in the residual unobliterated portion of the malpighian tuft

*Clinical picture*

As a rule, the lesions of focal endocarditic glomerulonephritis are so sparse or involve so small a portion of the malpighian tuft as to cause no apparent renal dysfunction As new lesions occur, mild to moderate, sporadic, recurrent or persistent hematuria is usually the only indication of their presence The hematuria must be differentiated from renal infarction. In occasional cases, the glomerular lesions may be so extensive as to interfere with renal function and may even lead to uremia. Of 23 cases of subacute bacterial endocarditis reported recently by Littman and Schaaf, 3 cases died with "renal failure" stated to have been produced by the focal glomerular lesions; in one of these patients, uremia was present. It remains to be determined whether or not antibiotic therapy of bacterial endocarditis will change the incidence of the various renal lesions associated with this disease

*Pathology*

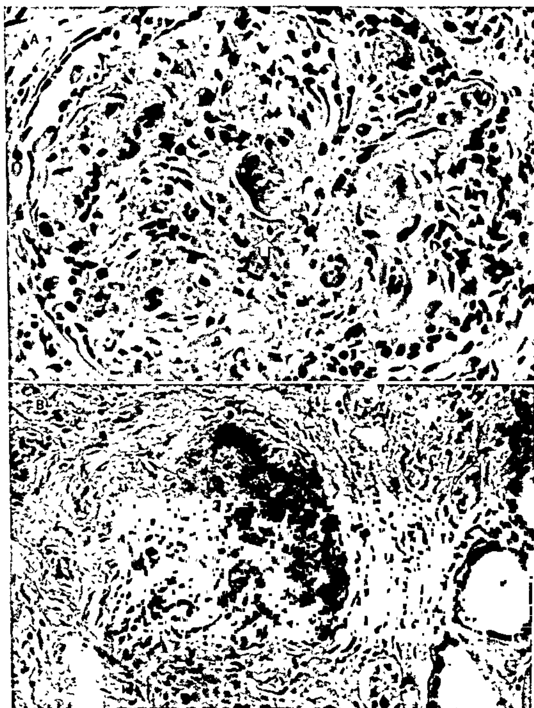
*Gross appearance.* Grossly, the kidneys may appear quite normal If the lesions are extensive, the kidney may be indistinguishable from that of acute diffuse glomerulonephritis, that is to say, it may be swollen, the cortex may be thickened and edematous, and the surface may be mottled with petechiae (plate 85 A)

*Histologic Appearance.* The lesion of focal endocarditic glomerulonephritis naturally varies with its duration. The earliest phase is characterized by a more or less circular focus of fibrinoid degeneration of collagen limited usually to one or occasionally two segments of the malpighian tuft and rarely involving the entire tuft The hyaline mass consists actually of a fibrinoid coalescence of a few glomerular capillaries with their appertaining endothelial and epithelial cells Often there is adherence of the lesion to Bowman's capsule. The endothelial or epithelial cells immediately adjacent to these foci may be swollen and basophilic very much as a regenerating tubular epithelial cell. Detailed study of the periphery of the lesion, especially at its junction with the adjoining portion of the tuft, discloses transition stages of capillary walls intermediate in degree between the fibrinoid mesh of capillaries constituting the lesion and the unaltered ones of the remainder of the tuft (plates 85 B, 86). Silver stains, here too, reveal the argyrophilic fibers of the distorted glomerular capillaries (plate 86). Bacteria are very rarely found in these lesions.

The acute lesion, brightly eosinophilic and with a paucity of cells, becomes organized to form a densely hyalinized, hard collagenous segmental mass maintaining the essential configuration of the original lesion (plate 85 B). There appears to be no credible evidence to support the impression that the pathogenesis of the acute lesion is different from that of the healed one, contrary to other reports (e g Bell) Incidentally, in interpreting the argyrophilic fibers it must be remembered that fibrils in tissue undergoing collagenization may, in the presence of fibroblasts, show an argyrophilia that could be confused with the argyrophilia of degenerated collagen. This same problem obtains in the evaluation of changes in cardiac valvular verrucae (Allen). However, hematoxylin-eosin stained sections permit easy differentiation of a relatively acellular necrotic focus of fibrinoid material from a focus showing organization by healthy fibroblasts

The lesion of focal endocarditic glomerulonephritis may spare the tuft altogether and involve merely the afferent arteriole in isolated instances. The quality of the fibrinoid alteration of the afferent arteriole in such instances is identical with that of the tuft itself It is remarkable how little alteration occurs in those glomeruli in which the lumen of the corresponding afferent arteriole is severely compromised by the swollen necrotic arteriolar wall. Thrombosis is rarely seen in these lesions either of the arteriole or of the glomerular capillaries, although it is said to be characteristic of the acute lesion (Bell). Occasionally small crescents arise between the lesion and Bowman's capsule.

The portions of the tuft not specifically involved by the lesion are often altogether unaltered but in some instances take on the appearance of exudative or proliferative glomerulitis Again, as in lupus erythematosus the number of glomeruli involved by this peculiar




FIGS. A AND B *Glomeruli from cases of chronic sclerosing glomerulonephritis with acute exacerbation* The exacerbation is represented by a focal fibrinoid degeneration (arrow) of the collagen of previously scarred glomeruli, indicating that such fibrous areas are not unreactive

lesion may be few or many and the signs and symptoms obviously vary accordingly In about 8 per cent of cases a sufficient number of glomeruli are involved extensively enough to cause renal failure. However, the glomerular damage is enough to cause frequent hematuria, and red blood cells may be found frequently in both the proximal and distal tubules in this condition The formation of masses of hemoglobin in the distal nephron from laked red blood cells (plate 86 B) must not be confused with hemoglobinuric nephrosis. If the lesion is of some duration and severity, it may be associated with the type of tubular atrophy, interstitial fibrosis and focal interstitial inflammation that is seen in subacute or chronic glomerulonephritis

*Reasons for nonembolic nature of focal endocarditic glomerulonephritis*

It is generally taught that the lesions of focal endocarditic glomerulonephritis are produced through embolization of particles of vegetations of subacute bacterial endocarditis And, to be sure, the lesion is practically pathognomonic of subacute bacterial endocarditis although a few cases have been recorded in its absence Nevertheless, there are several convincing reasons for doubting the embolic pathogenesis of this lesion

In the *first* place, bacteria are found with extreme rarity in these glomerular lesions. *Second*, the vegetations of acute bacterial endocarditis are often as large and as friable and about as prone to embolize as those of the subacute variety Nevertheless, in cases of acute bacterial endocarditis (that is, bacterial endocarditis of less than six weeks duration) the lesions of focal endocarditic glomerulonephritis practically do not occur The same situation obtains in Libman's "bacteria-free stage of subacute bacterial endocarditis." *Third*, focal endocarditic glomerulonephritis, as stated, has been reported, although rarely, to be sure, in the absence of subacute bacterial endocarditis or other sources of emboli *Fourth*, it would seem most unlikely for a vegetation to throw off hundreds of small emboli of about equal size into the general circulation, and for them to land in one organ to the practical exclusion of others. Finally, in instances of true septic emboli, clusters of bacteria often land in a glomerular capillary but fail to produce this lesion. Similarly, the inoculation of solid particles, as of potato agar, into the blood stream of an animal does not provoke this type of lesion.

*Nature of focal endocarditic glomerulonephritis*

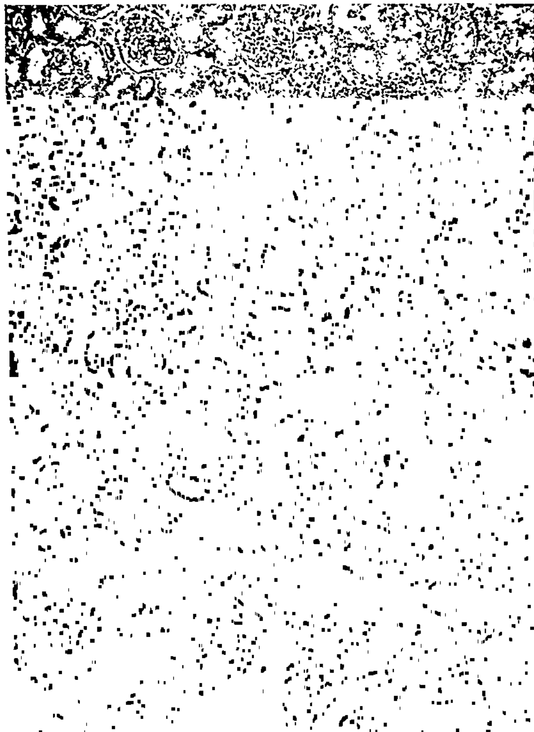
It is therefore our impression that the lesion of focal endocarditic glomerulonephritis represents an intrinsic fibrinoid reaction principally of glomerular capillaries but also of afferent arterioles This reaction is not produced by the direct local action of bacteria but is very likely an immuno-allergic response presumably to the antigenic products of the bacteria and occasionally other allergenic agents, as in periarteritis nodosa. Such a concept explains more reasonably the absence of these glomerular lesions in acute bacterial endocarditis of a duration of six weeks or less, inasmuch as apparently greater time is required to set the stage for such an immuno-allergic response in this disease

The occurrence of dense collars of plasma cells about some of the involved glomeruli is consistent with and suggestive of an immuno-allergic reaction rather than a reaction to the direct local infiltration of bacteria. This same principle applies to other infectious diseases, including the rickettsial diseases No such capillary lesion similar to focal endocarditic glomerulonephritis is found in other organs, but then, neither is the "wire-loop" lesion of disseminated lupus erythematosus, the capillary diabetic glomerulosclerosis or the capillary lesions of glomerulonephritis found in other organs. The selective localization of these lesions to glomerular capillaries has been at-

FIG A *Acute focal exudative glomerulonephritis (Staphylococcus aureus septicemia)* The single affected glomerulus is in sharp contrast to the other uninvolved glomeruli No bacteria were demonstrable in the section.

FIG B *Acute focal necrotizing glomerulonephritis* due to *Staphylococcus aureus* sepsis. No bacteria were demonstrable in the section.

PLATE 83. ACUTE FOCAL GLOMERULONEPHRITIS ("INFEKTNEPHRITIS")




(Legends on facing page)

tributed to the relatively greater amount of blood that bathes glomerular in contrast to other capillaries, but this is probably not the complete answer

## Disseminated Lupus Erythematosus

Disseminated lupus erythematosus is characterized clinically by its rarity in males, prolonged fever, arthralgia, dysphagia, cutaneous telangiectatic rash especially of the cheeks and nose and the manubrial area of the chest, erythematous patches in the mouth, cardiac murmurs, pleuritic and peritoneal pain, leukopenia and thrombopenia Remissions and exacerbations are common The blood Wassermann test may give inconsistent results and may become falsely positive or anticomplementary, during the exacerbations The gamma globulins of the blood are usually increased (Walker and Benditt) The "L E" cells are commonly present in the marrow and occasionally even in the peripheral blood (plate 96 C, D)

The disease runs its fatal course over a period varying from weeks, months, or years Permanent recovery is said to occur (Baehr and Pollack) but such instances must be exceedingly rare The remarkable selectivity of the female in this disease presupposes some hormonal linkage even though many of the histologic reactions are similar to those of allergy. Naturally, there comes to mind the fibrinoid reaction of vessels in animals treated with desoxycorticosterone (DCA) and related compounds in various situations of stress A few instances of disseminated lupus erythematosus have occurred in males; these patients had no overt endocrinologic abnormalities

In any individual patient only a few of the signs and symptoms listed above may occur, even *the rash may be completely absent* throughout the course of the disease. The clinical differential diagnosis of disseminated lupus erythematosus depends on the particular combination of signs and symptoms that are present. The list of such differential diagnoses includes rheumatic fever, subacute bacterial endocarditis, periarteritis nodosa, diffuse glomerulonephritis, scleroderma, dermatomyositis, trichinosis, and obscure infectious diseases, obstructing lesions of the esophagus and even surgical diseases of the abdomen because of the pain from the serositis

### *Renal Lesions in Disseminated Lupus Erythematosus*

The kidneys of disseminated lupus erythematosus are generally somewhat larger than normal Their surfaces are usually smooth but occasionally they are irregularly scarred and diffusely mottled with greyish and hemorrhagic areas or with petechial hemorrhages so as to resemble malignant nephrosclerosis or a form of acute diffuse glomerulonephritis (plate 88).

*Histologically the tubules show very little* change although in some instances hydropic vacuolization and marked hyaline droplet degeneration of the proximal tubles, often associated with slight fatty change, are prominent Renal arteritis, simulating periarteritis nodosa, or any other arteritis is uncommon, contrary to the implication of the generally accepted cliché that the condition represents a diffuse vascular disease. Focal interstitial infiltration with lymphocytes, plasma cells and histiocytes is frequently present. Focal fibrinoid degeneration of stromal collagen is rarely found in the kidney in contrast to the incidence in the myocardium.

#### *"Wire-loop" glomerulitis of disseminated lupus erythematosus*

In about 60 per cent of the cases of disseminated lupus erythematosus there is found a lesion of the glomeruli that is essentially pathognomonic of this disease, but with exceptions as will be indicated (plates 89, 90).

The glomerulitic lesions of lupus erythematosus is characterized by a focal, bright, acidophilic, homogeneous, generally nongranular *thickening of one or more segments* of the glomerular capillaries. Even in the flat plane of a section, the affected segments appear rounded by the usual presence of a fine highlight in the loop of the "wire." Bowman's capsule may show a similar focal fibrinoid degeneration Unlike the less strikingly eosinophilic, evenly diffuse change in membranous glomerulonephritis (plate 91 A), the capillary wall of the lupus lesions may *abruptly* thicken

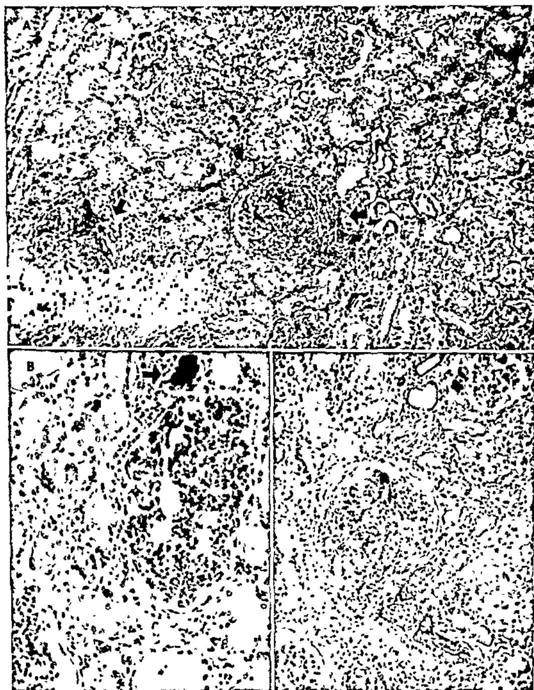



FIG A *Acute focal proliferative and necrotizing glomerulonephritis* (arrows) attributed to sulfathiazole therapy Note the normal glomeruli in striking contrast to the altered glomeruli

FIG B *Acute focal exudative glomerulonephritis* in staphylococcus sepsis with bacterial embolus in afferent arteriole (arrow) This form of focal glomerulitis, unlike focal endocarditic glomerulitis, appears to be due directly to bacteria

FIG C *Acute focal glomerulonephritis* with appertaining tubular necrosis following therapy of subacute bacterial endocarditis with bacitracin

into an intralumenar mound, often mistaken for a fibrinous thrombus This mound is really a form of verrucal capillaritis after the fashion of verrucal endocarditis or verrucal endocardiosis (Allen and Sirota), or the verrucal arteriolitis of typhus fever (Allen and Spitz) The fibrinoid material composing the wire-loop may take the stain for fibrin on the one hand or may stain as collagen does in its various intermediate stages of degeneration In other words, with a Mallory-Heidenhain stain, the lupus lesion, even in a single segment, may vary from red to orange to blue, depending on the degree of degeneration of the capillary wall Its affinity for silver is also variable but often appreciable (plate 244 D) This, too, is in harmony with the behavior of altered collagen or reticulin.

The wire-loop lesion may be associated with an otherwise normal tuft, or a tuft may be the seat of exudative or necrotizing glomerulitis, so severe as to show karyorrhectic distintegration of nuclei (plate 89 A) Capillary lesions corresponding to the wire-loop changes are not found in organs other than the kidneys.

As with other forms of focal involvement of glomeruli, for example, focal endocarditic glomerulonephritis or diabetic glomerulosclerosis, the degree of interference with renal function is obviously dependent on the number and extent of glomeruli involved In other words, it can not be said categorically that the renal lesions in disseminated lupus erythematosus always lead to renal insufficiency In some instances, the renal lesions are found only in isolated glomeruli If most glomeruli are involved, renal insufficiency develops, as it does in about 39 per cent of cases Some of these cases of disseminated lupus erythematosus with pretty nearly generalized glomerular involvement have in the past been classified merely as nonspecific acute or chronic diffuse glomerulonephritis

Rarely, disseminated lupus erythematosus may be complicated by nonspecific diffuse glomerulonephritis. Rarely, too, lesions indistinguishable from the "wire-loop" changes are noted in eclampsia, scleroderma, glomerulonephritis, and malignant nephrosclerosis (plate 98).

In connection with the clinical diagnosis of the involvement of the kidney by lupus erythematosus, it is worth noting Krupp's observation that the Addis count in these cases revealed excessive red blood cells, red blood cell casts, fat oval bodies, epithelial and fatty casts, and large renal failure casts In other words, the sediment is said to represent a telescoping of the findings of the three stages of glomerulonephritis

### *Extra-renal Lesions in Disseminated Lupus Erythematosus*

Because of the confusion regarding the terminology, the pathogenetic and morphologic concepts of disseminated lupus erythematosus, as well as the details of the histologic quality of the lesions of the kidney as opposed or as related to lesions in other organs, a summary of these lesions might be of some use It is desired especially to try to define in this manner the various changes that occur in collagen and are important for the understanding of glomerular pathology.

One fact is immediately clear: although collagen and, in certain ways, reticulin have a limited range of histologically visible reactions to stimuli, there is nevertheless a sufficient number of categories of histologic change in this tissue that can be sharply defined and segregated. It is not at all trite to emphasize that just as not all hyaline looks alike, so not all fibrinoid degenerations of collagen look alike And however nice these distinctions between the various forms of collagenous alteration

FIG A *Focal endocarditic glomerulonephritis* showing characteristic petechial hemorrhages This kidney would require differentiation grossly particularly from acute diffuse glomerulonephritis (plate 54) as well as from malignant nephrosclerosis (pate 211A)

FIG. B *Focal endocarditic glomerulonephritis*, from a case of subacute bacterial endocarditis The

## PLATE 85. Focal Endocarditic Glomerulonephritis (Focal "Embolic" Glomerulonephritis)




(Legends on facing page.)

may be, they are not so veiled as to have their categorical nature concealed by adequately prepared routine sections stained with hematoxylin-eosin This is not to say that special staining and fixing methods should not be used for definitive investigative studies (After all, the use of various silver, trichrome, lipid, glycogen and enzymatic stains, tryptic digestion and different fixatives such as xanthydrol, Zenker's and Regaud's solution, for the preparation of sections photographed and studied for this book demonstrates their specific usefulness ) This *is* to say, however, that for practical diagnostic purposes, routine sections serve in the instance even of the challengingly delicate and much mimicked changes of the collagenous diseases What is required is an accurate visual evaluation of the granularity, acidophilia, homogeneity, location, shape, and form of the fibers, as well as of the accompanying *inflammatory changes, or the lack of* them

*Skin*

Three types of cutaneous lesions occur in lupus erythematosus These are (1) chronic or discoid, (2) acute and (3) combined acute and chronic.

The *chronic or discoid* form of lupus erythematosus most often occurs in the skin over the malar regions and bridge of the nose but may also be found in the skin of other parts of the body It is a scaly, red, indurated lesion The histologic features include (1) alternating acanthosis and atrophy of the epidermis, (2) liquefaction degeneration at the dermo-epidermal junction, (3) dense collections of mononuclear cells, mostly lymphocytes, usually in the mid-dermis, (4) superficial hyperemia, (5) keratotic plugging of follicles and (6) spotty parakeratosis (scaling) (plate 93). *Changes in collagen and blood vessels are not part of this picture* although statements to the contrary are in the literature Chronic or discoid lupus erythematosus is rarely associated with the disseminated lesion.

The *acute lesion* of lupus erythematosus occurs on the face and upper chest particularly but may also involve the hands and mucous surfaces Histologically it is characterized by a marked exaggeration of the liquefaction degeneration seen in the chronic form. The corium in this region is edematous and acidophilic, especially immediately adjacent to the epidermis where it may form an acidophilic band. The inflammatory cells include polymorphonuclear leukocytes, the nuclei of which tend to be elongated and otherwise distorted and fragmented (plate 93 B) Infrequently there is *patchy fibrinoid degeneration of the dermal* collagen and of the wall of an occasional vessel If the diagnosis of lupus erythematosus, acute or chronic, were to rest on the finding of vascular degeneration in the skin, most of the cases would remain undiagnosed.

The *acute and chronic form* of lupus erythematosus is characterized by the *combined* features of the two types just described In general it is impossible to distinguish histologically between the self-limited acute changes produced in a lesion of discoid lupus erythematosus by exposure to ultraviolet light, and those acute changes that occur as part of the systemization of the disease. Prognostication in such cases is guided by the facts that dissemination of the disease occurs relatively rarely in males, and rarely also as a complication of the chronic disease. Furthermore, clinical evidence of involvement of organs

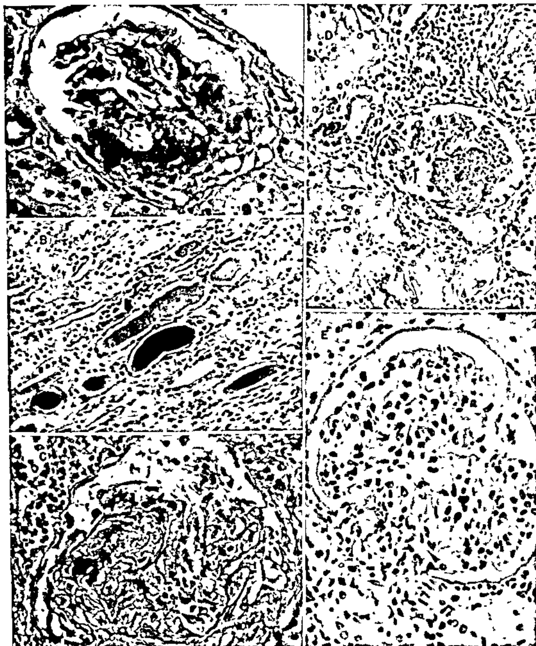
FIG A *Focal endocarditic glomerulonephritis* illustrating the early phase of fibrinoid necrosis in which the capillaries have not yet coalesced

FIG B *Hemoglobin casts* in focal endocarditic glomerulonephritis as a result of red blood cells having been fragmented in the tubules

FIG C *Modified Bielschowsky's silver stain* of focal endocarditic glomerulonephritis showing the congeries of silver fibers representing the residue of altered glomerular capillaries

FIG D *Focal endocarditic glomerulonephritis* showing the acute coalescent phase of fibrinoid degeneration of a portion of the malpighian tuft; the remainder of the tuft is essentially normal

FIG E *True embolic glomerulonephritis* in bacterial endocarditis showing embolus and polymorphonuclear leukocytic reaction This lesion is obviously different from focal endocarditic glomerulonephritis




(Legend on facing page)




FIG A *Focal endocarditic glomerulonephritis* in which the lesion is made up of a cluster of necrotic glomerular capillaries with fibrinoid alteration of their walls and with partial secondary thrombosis of their lumens The thrombosis is altogether secondary and may or may not be present The fibrinoid necrosis of the capillary walls is the primary alteration (From a case of subacute bacterial endocarditis )

FIG C *Acute exudative and proliferative glomerulonephritis* of acute bacterial endocarditis Focal endocarditic glomerulonephritis is responsible for about one third of the cases of uremia in subacute bacterial endocarditis

FIG B *Diabetic glomerulosclerosis* which superficially
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not difficult to distinguish The argyrophilic pattern of each is altogether different (see plates 243 and 244)

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glomerulonephritis is uncommon in subacute bacterial endocarditis except in the so-called "bacteria-free" stage




Figs. A and B *Kidney of disseminated lupus erythematosus* showing the hemorrhagic, mottled, and irregularly pitted appearance of the cortex

other than skin would very likely be present in the disseminated disease

*Heart*

The most striking cardiac lesion in disseminated lupus erythematosus is an endocarditis that has been called Libman-Sacks disease, or atypical verrucous endocarditis This lesion occurs in about 30 per cent of cases of the disseminated disease Grossly the vegetations tend to be friable and uniform in size in a given case, but may vary in different cases from a lesion that is hardly visible to one 4–6 mm in amplitude They have a peculiarity in their occasional but by no means invariable occurrence in unusual locations such as the pockets or angles of the valves The remainder of the vegetation is found near the line of closure as in the other varieties of endocarditis.

Histologically, the lesions are usually recognizable particularly by the characteristic hematoxylin bodies which are present also in other organs, and the prominent fibrinoid degeneration of the endocardium of the valves and chamber walls (plate 95 A) The hematoxylin bodies are obviously compressed and distorted nuclear residues, so that it is hardly surprising that they contain desoxyribosenucleic acid An incidental bacterial endocarditis frequently complicates the specific lesion terminally (Klemperer et al ), because it offers a nutrient nidus for the growth of bacteria that happen to be in the blood stream (Allen and Sirota)

Other cardiac lesions of this disease include a characteristic fibrinoid degeneration of interstitial collagen of the myocardium and of the epicardium (plates 95 B, 96 A).

*Spleen*

Another almost pathognomonic change in disseminated lupus erythematosus is the concentric lamination of rings of hard dense collagen about the central arterioles of the spleen (plate 94). This change represents a collagenization of the normal fine reticulin, and is rarely seen in a full-blown state in any other disease, although miniature forms have been noted This form of collagenization is quite distinctive from the soft, acidophilic, fibrinoid change in the glomerular capillaries, or in the interstitium of the myocardium. The splenic change occurs in about 95 per cent of cases of disseminated lupus erythematosus

*Lymph nodes*

No specific lesion is present in the lymph nodes which may, however, show areas of necrosis of the type seen in serum sickness, other allergic states, and in some infectious diseases, such as typhus fevers (Allen and Spitz) Infrequently, laminations of collagen about arterioles are found resembling those of the spleen (plate 96 B).

*Blood vessels*

Blood vessels of approximately the caliber of renal interlobular arteries may be altered by varying degrees of fibrinoid alteration, subendothelial proliferation of fibroblasts, and perivascular collection of mononuclear cells so as to simulate periarteritis nodosa These vascular changes may occur in a variety of organs including the choroid plexus of the brain. Impressive as the histologic change of an individual lesion may be, however, the fact is that many cases of disseminated lupus erythematosus occur without any such vascular

FIG A. *Disseminated lupus erythematosus* Glomerulus shows characteristic fibrinoid swelling and degeneration of capillary walls, endothelial proliferation, exudation and karyorrhexis of leukocytes and beginning proliferation of capsular epithelium The fibrinoid swelling is often so marked as to simulate thrombi

FIG B *"Wire-loop" lesion* in upper half of photograph is almost pathognomonic of disseminated lupus erythematosus but may occasionally be seen in possibly related diseases, such as scleroderma, dermatomyositis and eclampsia The "wire-loops" are focal, the remainder of the tuft shows the picture of acute exudative glomerulitis

FIG C *"Wire-loops"* may swell and form vertical projections which have been mistaken for "hyaline thrombi " The lesion illustrated here is unusually marked, the more characteristic "wire-loops" are shown in figure B




(Legends on facing page)

lesions being demonstrable, at least in a routine number of sections Moreover, in none of the 22 cases personally examined were there lesions of sufficient numbers of arteries in enough organs to begin to account for the clinical picture or the deranged physiology The renal capillary damage is, of course, not included in the scope of this statement. It is this same cliché of *diffuse vascular disease* that has been used to explain the altered physiology of other diseases, for example, scrub typhus, even though arterial disease of the viscera is a rare histologic finding

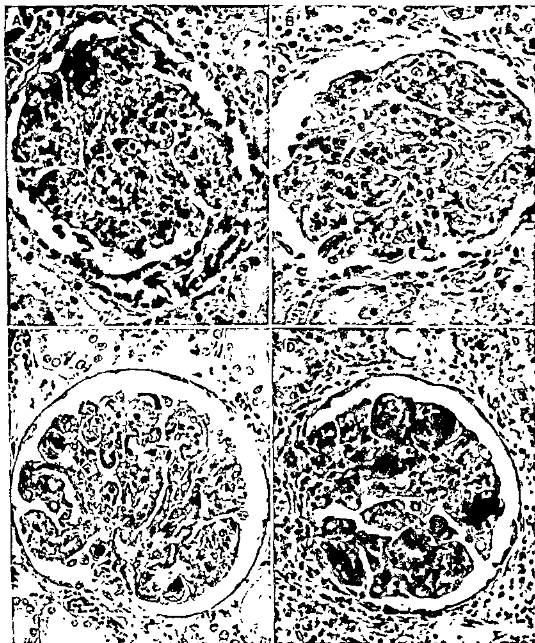
*Miscellaneous*

The serosal surfaces and areolar tissue may be the sites of fibrinoid alteration which may produce symptoms depending on the location Focal inflammation of skeletal muscle is usually mild but at times may be intense The routine sections of bone marrow do not show significant change, but recently a special "L E" or Hargraves' cell has been described, which is found abundantly in the marrow, particularly in the severest stage of the disease These cells may be found also in the peripheral blood in grave cases The "L.E." cell itself is not a polymorphonuclear leukocytes as was originally and subsequently reported The cell is mononuclear and resembles a lymphocyte with engulfed or accoladed polymorphonuclear leukocytes, often in rosette formation (plate 96 C, D) If the plasma from a patient with disseminated lupus erythematosus is added to the heparinized marrow from a normal person, or even from a dog, cells indistinguishable from "L E" cells are produced This procedure facilitates the finding of the cells The phenomenon is attributed to specific gamma globulins within the blood, although thus far, a false positive has been noted in a case of multiple myeloma

*Common Denominators of Lupus Erythematosus, Scleroderma and Dermatomyositis*

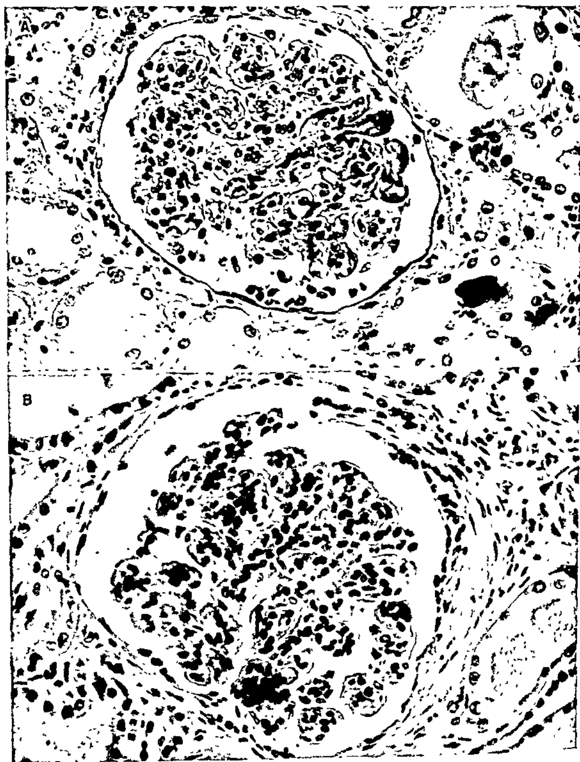
The clinical and pathologic features of disseminated lupus erythematosus, scleroderma and dermatomyositis have been so intimately identified with each other that papers on therapy and pathology consider them interchangeably in all basic respects This point of view has developed from the assumption either that all three are diseases of collagen, or that all three are diffuse vascular diseases Are such assumptions loose and convenient clichés or is there as much in common in the histologic picture of these diseases as is generally assumed? Actually, in scleroderma and disseminated lupus erythematosus, there *are* changes in the collagen, but the qualitative difference in the dense sclerosis of the cutis and of the submucosa of the esophagus and intestine of scleroderma (plate 97) from the fibrinoid degeneration of the serosa in lupus erythematosus warrants thinking in terms of basic dissimilarity. Although the characteristic "wire-loop" glomerular change has been observed in scleroderma (plate 98 A, B), it is a rare finding in this disease—about as rare as it is in the other exceptional cases in which it occurs. The peculiar edema and lamination of the intima of the renal interlobular arteries (plates 98 C, D, E, F) is an infrequent finding in scleroderma that resembles a change of malignant nephrosclerosis and does not suggest disseminated lupus erythematosus. The dense myocardial fibrosis of scleroderma is altogether different from the interstitial fibrinoid degeneration of the myocardium of disseminated lupus erythematosus Finally, the mere fact of the existence of the combination of cutaneous and visceral collagenous changes in two diseases is not tantamount to establishing their essential identity, although the literature tends to indicate that it is

The relationship of dermatomyositis to disseminated lupus erythematosus and scleroderma appears to have been built on an even more specious basis. In dermatomyositis, changes occur in the skin, muscle, nervous system, and, rarely, in the arteries The cutaneous changes are altogether nonspecific, in sharp contrast to the usually diagnostic changes of scleroderma and lupus erythematosus (plate 99A). The myositis of dermatomyositis is often extensive, but, again, quite nonspecific (plate 99 B). Visceral vascular changes are, also, simply rare, although they do resemble the few visceral arterial lesions of lupus erythematosus. The neural changes, principally demyeliniza-




These photomicrographs show various degrees of glomerular alteration in disseminated lupus erythematosus including "wire loop" formation, verrucal swelling of walls of glomerular capillaries (so called "hyaline thrombi") and glomerulitis with karyorrhexis of endothelial cells

PLATE 92 DIFFERENTIAL HISTOLOGIC DIAGNOSIS OF LESIONS OF DISSEMINATED LUPUS ERYTHEMATOSUS



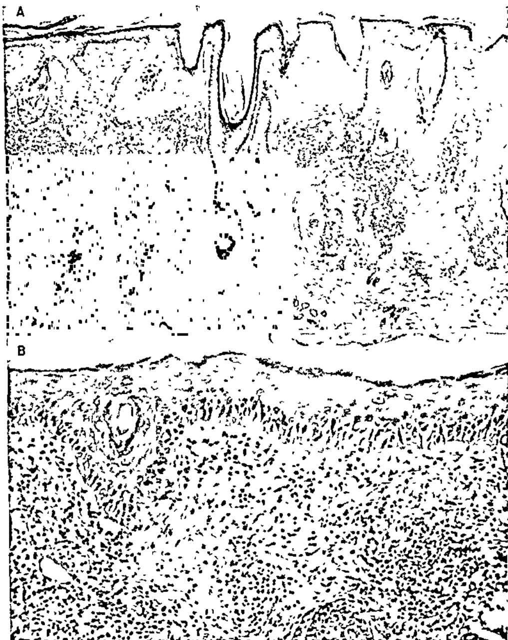



Fig A *Skin in chronic discoid lupus erythematosus* is diagnosable by histologic changes which consist of (1) compact masses of lymphocytes in mid-dermis or about appendages, (2) alternating epidermal acanthosis and atrophy, (3) keratotic plugs of follicles, (4) liquefaction degeneration of basilar layers, (5) subepidermal hyperemia, (6) focal parakeratosis

Fig B *Skin in acute disseminated lupus erythematosus* superimposed on discoid lupus erythematosus The acute changes are indicated by the exaggerated liquefaction degeneration of the basilar layers, the prominence of the acidophilic cytoplasmic change at the junction of the epidermis and dermis the fibrinoid degeneration of the collagen of the upper dermis the nuclear distortion of subepidermal inflammatory cells and the superficial hyperemia Contrary to the general impression, degenerative or inflammatory vascular changes are usually absent in the skin in these cases

along with their antecedent phase and sequelae are the conditions of prime concern.

Hypertension and albuminuria together constitute definitely abnormal findings in pregnancy. Static hypertension and albuminuria, however, do not constitute preeclampsia. Generalized edema without hypertension is present in about 75 per cent of otherwise normal pregnant women (Fink). *The edema, of itself, is* rarely serious although it may be responsible for headaches, scotomas, and even convulsions and coma in isolated instances (Dexter and Weiss). The edema does not damage the fetus (Dexter and Weiss) and does not alone indicate a toxemia of pregnancy. It may be caused by hypoproteinemia, increased venous or capillary pressure, cardiac failure, anemia, vitamin B deficiency, myxedema, or excessive intake of sodium salts. An endocrine or possibly a renal factor may be at fault, but, nevertheless, edema as an isolated feature, is not of great significance during pregnancy. It is the association of edema with hypertension that begins to take on great importance.

*Preeclampsia and Eclampsia*

*Preeclampsia* occurs in the latter half of pregnancy, *often at about the 34th week*, it may occur also in the postpartum period. *Eclampsia* rarely begins later than 24 hours postpartum. This toxemia complicates about 1 in 139 to 1 in 620 pregnancies. It occurs much more often in primiparas than in multiparas. Probably the chief reasons for this selective incidence is the failure of survival of many of the patients as well as the discouragement of subsequent pregnancies. Preclampsia or eclampsia may develop also in association with a hydatid mole (Page).

Preeclampsia is characterized by hypertension and albuminuria (both above pre-pregnancy level), generalized edema, headaches, nausea and vomiting, vertigo, visual disturbances, drowsiness, twitchings, coma, and, in the eclamptic stages, convulsions. The eyegrounds are usually normal but papilledema, hemorrhages, exudates and even retinal detachment may occur. Levels of urea and nonprotein nitrogen tend normally to be low in pregnancy and are usually within normal range in toxemias of pregnancy. The resemblance of these signs and symptoms to those of severe, acute diffuse glomerulonephritis (especially of the membranous type) with hypertensive encephalopathy is obvious.

This symptom complex of preeclampsia or eclampsia may develop *de novo* during pregnancy or may be superimposed in patients with *antedating hypertension and/or albuminuria* on the basis of preexisting renal disease. In the past, such patients have been placed in the grouped labeled "low kidney reserve." Their renal lesions might be one of several: chronic glomerulonephritis, chronic pyelonephritis, benign or malignant nephrosclerosis, anomalies (e.g., polycystic kidneys) and probably other diseases that significantly compromise renal function prior to pregnancy. Many of these patients have an uneventful course although the incidence of stillbirths and abortions is high in this group. However, about 5 per cent of such patients develop preeclampsia (Dexter et al.). Rarely, renal diseases producing hypertension, such as acute diffuse glomerulonephritis, may first occur during pregnancy without leading to preeclampsia (Dexter et al.). Pyelonephritis initiated during pregnancy is a common *evanescent and usually clinically unimportant* condition (Robertson).

*Sequlae of Toxemias of Pregnancy*

In patients with preeclampsia without preexisting *hypertension, the infant mortality* is about 5 per cent in the mild cases to 25 per cent in the severe ones (Peckham), in those with antecedent hypertension, the mortality is greater, ranging from 12 to 69 per cent (Corwin and Herrick). *The earlier in pregnancy* the preeclampsia develops, the greater is the infant mortality. The infants of preeclamptic and eclamptic mothers that survive the neonatal period suffer no demonstrable ill effects.

The maternal mortality *from preeclampsia* is about 1 per cent (Dieckmann and Brown), and from eclampsia, about 10 to 20 per cent (Stander). In these days of prenatal care, fortunately relatively few patients are permitted to deteriorate to *the stage of eclampsia*. The most frequent cause of death in eclampsia is left ventricular failure with pulmonary edema










FIG. A *Spleen in disseminated lupus erythematosus*, the surface of which is speckled with periarteriolar fibrous tissue in follicles

FIG. B *Concentric rings of periarteriolar fibrosis* of malpighian corpuscles of spleen a very common finding in disseminated lupus erythematosus and uncommon in other diseases

FIG. C *An early acute phase* of the lesion pictured in figure B In addition to the periarteriolar fibrosis, there is central fibrinoid degeneration and acute inflammation

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### *Sequelae of Toxemias of Pregnancy*

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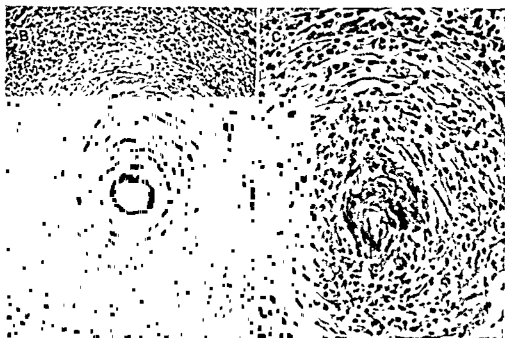




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FIG. C *An early acute phase of the lesion pictured* in figure B In addition to the periarteriolar fibrosis, there is central fibrinoid degeneration and acute inflammation




FIG A *Atypical verrucous endocarditis* of disseminated lupus erythematosus "Hematoxylin bodies" are present (arrows) within the necrotic collagen of the verruca

FIG B *Interstitial fibrinoid myocarditis* characteristic of disseminated lupus erythematosus Anitschkow myocytes, lymphocytes and a few polymorphonuclear leukocytes are intermingled among the long strands Distinction from Aschoff bodies is rarely difficult

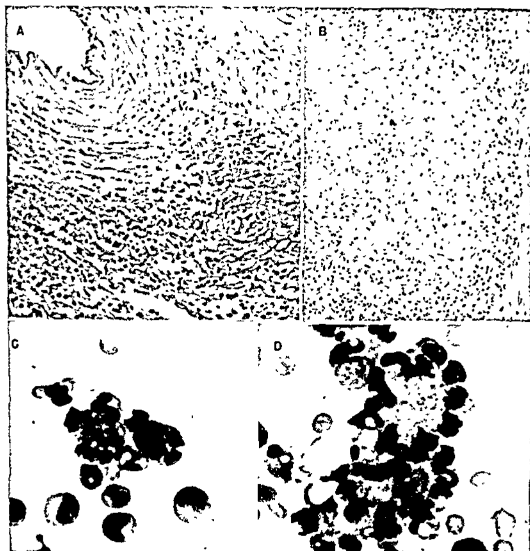



FIG A *Epicarditis* of disseminated lupus erythematosus with fibrinoid degeneration of fat

FIG B *Patchy necrosis of lymph node* in disseminated lupus erythematosus similar to that seen in allergic reactions and in some infections such as scrub typhus

FIGS C AND D "*L E*" *cells* from marrow The "L E" cell of disseminated lupus erythematosus is practically pathognomonic of disseminated lupus erythematosus It may be found in the peripheral blood, but is observed more easily in the marrow, especially of severely ill patients The phenomenon of the "L E" cell may be produced by adding the patient's serum to heparinized marrow, even to marrow of a normal human or dog The rosette of polymorphonuclear leukocytes about or within a mononuclear cell (probably lymphocyte) is especially characteristic.

Termination of the pregnancy is followed by rapid improvement in even the most desperate cases Despite this improvement, however, hypertension tends to persist even after milder episodes of preeclampsia and is responsible for a high percentage of deaths in the following years (Herrick and Tillman) About 25 per cent of patients with toxemias of pregnancy without preexisting hypertension are left with a permanent postpartum hypertension, about the same percentage of hypertensive patients who develop the toxemia of pregnancy acquire an aggravated postpartum albuminuria and hypertension (Teel and Reid, Herrick and Tillman; Dieckmann and Brown) The vascular disease of essential hypertension appears to develop with greater frequency in patients with mild toxemias than in the eclamptic patients, as if the duration of the toxemia was more important than its severity in leading to this sequela However, it should be mentioned in this summary of the sequelae of the toxemias of pregnancy that there exists a range of opinion on the subject, including the impression that practically no evidence of residual renal damage caused by the toxemia persists (Schmeckel, Seitz).

*Pathologic Changes of the Toxemias of Pregnancy*

It is clear that renal disease may antedate the pregnancy and the toxemia, or it may be initiated during the pregnancy In either case, the same clinical symptoms of preeclampsia or eclampsia may result However, the renal changes will differ, and may be classified as follows·

- Renal lesions of preeclampsia and eclampsia antedating pregnancy
  - Chronic glomerulonephritis (most common)
  - Chronic pyelonephritis
  - Benign and/or malignant nephrosclerosis
  - Various anomalies of the kidney with reduction of renal reserve
- Renal lesions of preeclampsia and eclampsia initiated during pregnancy
  - Bilateral cortical necrosis
  - Acute diffuse membranous glomerulonephritis (common)
  - Acute proliferative, exudative or necrotizing glomerulonephritis
- Renal sequelae of preeclampsia and eclampsia
  - Chronic glomerulonephritis of various forms
  - Benign and/or malignant nephrosclerosis

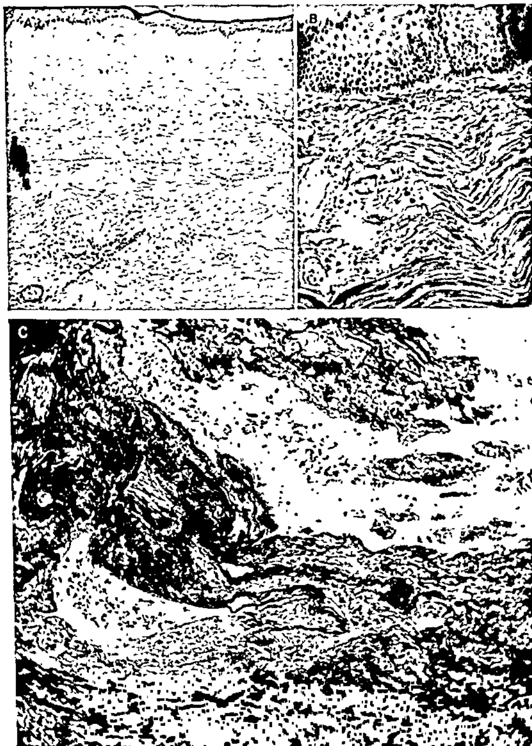
*Of all the lesions listed, the acute diffuse* membranous glomerulonephritis is of particular interest; the other lesions are discussed in their respective sections It may be impossible to *predict, from the immediate clinical picture,* which variety of acute renal lesion will be found. Clinical data on the renal background of the patient are usually necessary for such *diagnoses On the other hand, there is* a distinctive variety of membranous glomerulonephritis which, on histologic grounds, permits the diagnosis of toxemia of pregnancy to be *made This lesion was emphasized* particularly by Lohlein and Fahr, and in this country by Bell, and is illustrated in plate 100. It consists of ischemic glomeruli with diffusely and uni*formly thickened basement membranes,* again, easily detected with routine stains, such as hematoxylin-eosin Endothelial cells may or may not be increased and swollen Occasionally, the membranous glomerulonephritis may be associated with focal fibrinoid, eosinophilic alteration of glomerular basement membranes so as to simulate the glomerular "wire-loop" change of disseminated lupus erythematosus plate 102 B, C) Other vascular and interstitial changes are inconspicuous The tubules are usually not seriously altered histologically, they may show hydropic, fatty, or hyaline degeneration and, infrequently, focal necrosis

The proliferative, exudative and necrotizing forms of acute diffuse glomerulonephritis, or benign or malignant nephrosclerosis, or pyelonephritis may also occur with eclampsia and are not distinguishable from the corresponding *lesions seen apart from pregnancy* (plate 100

Fig A *Diffuse scleroderma of skin* showing the dense, homogenized collagen of the cutis, the atrophy of the epidermis, and the melanotic pigmentation of its basal layer

Fig B. *Submucosal fibrosis of the esophagus* in a case of scleroderma The fibrosis may produce the clinical picture of peptic ulcer or esophageal obstruction

Fig C *Pulmonary cysts* in scleroderma characterized by marked elastosis (*Courtesy of S Aronson* )




(Legend on facing page.)

A). Bilateral cortical necrosis is considered separately (page 472).

The *changes in the liver* in preeclampsia and eclampsia are diagnostic when they consist of: periportal and subcapsular hemorrhage, necrosis of hepatic cells at the periphery of the lobules, fibrinoid swelling of the basement membranes of Disse's space with marked hyperemia particularly in the periportal regions, and with occasional fatty infiltration of hepatic cells; and increased periportal lymphocytic reaction (plate 102 D) The hepatic change occurs in about 50 per cent of cases of eclampsia (Fahr) and may occur also in preeclampsia. The possibility that the hepatic changes may have a pathogenetic bearing on the renal lesions as in other hepatorenal diseases, cannot yet be dismissed.

The *placenta* in these toxemias tends to separate prematurely, to have an increased number and size of infarcts, and to show accelerated aging of the villi. Many observers attribute the toxemia of pregnancy to the placental infarcts and the toxic substances they cause to be liberated The fact that signs and symptoms of the toxemia usually abate immediately after the pregnancy is terminated, suggests that toxic placental products may indeed spark the whole condition.

### *Relationship of Pregnancy Glomerulonephritis to Chronic membranous Glomerulonephritis ("Lipoid Nephrosis")*

*Acute membranous glomerulonephritis* is found in the vast majority of preeclamptic and eclamptic patients This lesion was found in 51 of 52 cases in Bell's series. This form of glomerulonephritis is histologically closely related *to chronic membranous glomerulonephritis* and probably histologically identical with its acute stage It will be recalled (page 154), that *chronic membranous glomerulonephritis* is characterized by the nephrotic syndrome, that is, by abundant albuminuria, marked edema *and by hypoproteinemia with hypercholesteremia*, hypertension may or may not be present. Correspondingly, the clinical picture of pre*eclampsia with the acute membranous glomerulonephritis* is similar in its basic respects to that of the nephrotic syndrome of relatively short *duration. Hematuria is absent or mild*

Albuminuria, edema and hypoproteinemia are part of the symptom complex of the toxemia of pregnancy in which the acute membranous glomerulonephritis is found. The fact that the hypercholesteremia is not especially marked over that of normal pregnancy, or that the degree of hypoproteinemia cannot always be directly correlated with degree of edema, or that hypertension occurs almost constantly, does not invalidate the essential thesis. In other words, the almost diagnostic acute membranous glomerulonephritis of preeclampsia and eclampsia—the glomerulonephritis described by Löhlein and later reemphasized by Bell—is really histologically and physiologically indistinguishable from the early stages of chronic membranous glomerulonephritis (i.e. the nephrotic form of glomerulonephritis or "lipoid nephrosis") occurring without pregnancy (plate 74 B) In both instances, the chief renal dysfunction is abnormal glomerular permeability to proteins, in both instances, renal failure is an inconspicuous feature. The chief point of divergence between the two entities is that the nephrotic type of syndrome of preeclampsia

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FIGS A AND B *"Wire-loop" thickening of glomerular capillaries in scleroderma* Such a picture is uncommon in cases of classical diffuse scleroderma in contrast to those with disseminated lupus erythematosus.

FIG C. *Kidney in scleroderma* showing marked *narrowing of the lumen of an interlobular artery and* "wire-loop" type of fibrinoid alteration of glomerular capillaries

FIG E *Cellular swollen intima of an interlobular* artery of kidney in scleroderma (Mallory-Heidenhain stain )

FIG D *Cellular edematous intima* of an interlobular artery of kidney in a case of scleroderma

FIG F *Marked narrowing and fibrinoid necrosis of afferent arteriole* of kidney in scleroderma The *vessels pictured in figures C, D, and E,* are of themselves strongly suggestive of the diagnosis of scleroderma although they resemble the vessels of malignant nephrosclerosis




(Legends on facing page.)

generally clears if the pregnancy is survived; in the case of chronic membranous glomerulonephritis, the course is usually hopelessly progressive except for transient periods of remission Without any question, termination of the pregnancy effects a restoration of the integrity of the swollen basement membranes of the glomerular capillaries If in most cases the mechanism of this restitution were known, we should then have a significant clue to the mechanism of repair of the similarly altered glomerular capillaries of chronic membranous glomerulonephritis

The more credible evidence indicates that at least hypertension persists in a large percentage of patients (25 per cent, Dexter and Weiss) who had not had this sign prior to the development of the toxemia of pregnancy It appears that even though the permeable capillaries of the acute membranous glomerulonephritis of preeclampsia and eclampsia may heal, the effect of the hypertension and the toxemia may leave its permanent stamp on the afferent arterioles It is believed that the residual afferent arteriolosclerosis is the factor responsible for the *persistence* of the hypertension in these instances. (The matter of *initiation* of the hypertension is something else again and will not be belabored here However, the recent suggestion of Hofbauer that hypertension in toxemia may be related to excessive activation of pituitary adrenocorticotropic hormone might be mentioned in view of the role in the production of renal arteriolosclerosis which Selye attributes to the adrenal corticoids.) The kidney illustrated in plate 102 E is an example of the effect of just such a sequence of events in an eclamptic patient with persistent and progressively mounting hypertension after gestation At autopsy, no significant renal lesion beyond marked afferent arteriolosclerosis was present, the glomerular tufts were remarkably intact

## Functional Glomerular Permeability

### *Benign Albuminuria*

There are many instances of individuals who, particularly near the age of puberty and during adolescence, excrete albumin for varying periods of time but do not have other evidence of organic renal disease. For example, 5 per cent of 50,000 otherwise healthy soldiers in training had albuminuria on arising, and after marching the incidence increased to from 7 to 14 per cent in a group of 200 (Maclean). This fact has long been known and corresponding figures of 4 per cent and 12 per cent were obtained by Leube in 1878 among soldiers on arising and after exercise Because the albuminuria frequently is present only in the first urine passed in the morning, the condition has been referred to as cyclic albuminuria However, the albuminuria in many cases is associated with a lordosis and so the name "orthostatic albuminuria" is applied. Even some of the instances of "cyclic" albuminuria are attributed to the assumption of the erect, lordotic posture upon getting out of bed, especially since the appearance of albuminuria could be delayed until evening by keeping the individual in bed all day.

Data on the percentage of cases of functional albuminuria in which posture is a factor vary considerably with the observer. According to some, all cases are related to posture; in direct contradiction, others have found that lordosis played no part in the functional albuminuria of a large group The over-all evaluation of the experience with this condition leads to the conclusion that posture does play a role in the albuminuria in a high percentage of cases The means by which the effect of changes in posture is detected appears to account for much of the discrepancy in the data

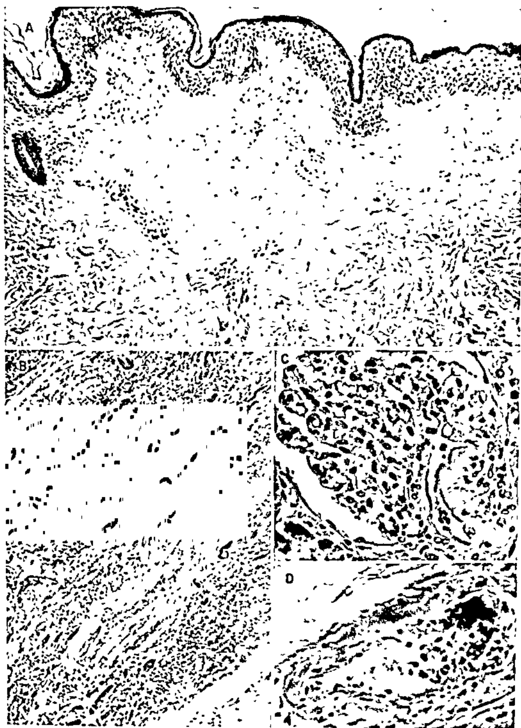
The total amount of protein lost in the urine

Fig A *Skin in dermatomyositis* almost always presents a nonspecific histologic picture Liquefaction degeneration, subepidermal edema and perivascular inflammation are usually observed in the degree shown here

Fig B *Myositis of dermatomyositis* with atrophy of muscle fibers and infiltration of lymphocytes, histiocytes and scattered polymorphonuclear leukocytes

Fig C *Acute focal glomerulitis* from a case of dermatomyositis with thrombosis of an afferent arteriole

Fig D *Fibrinoid arteritis* (periadrenal) in case of dermatomyositis




(Legends on facing page.)

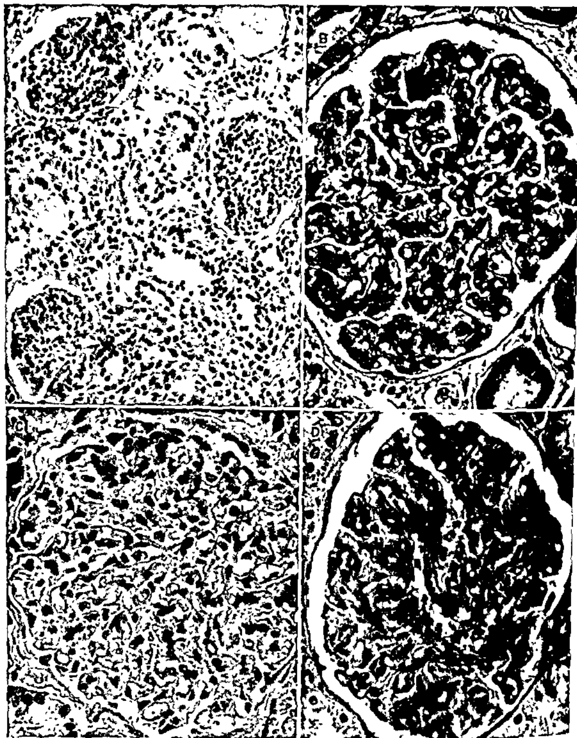



FIG A *Acute proliferative glomerulonephritis* associated with clinical eclampsia This patient was 16 years old and in her last month of pregnancy (A F I P Acc 100491)

FIG C *Acute membranous glomerulonephritis* of eclampsia showing glomerular ischemia, decreased cellularity and membranous thickening of the capillary walls intermediate in quality between those of figure B and figure D

FIG B *Acute membranous glomerulonephritis* of eclampsia with ischemia, and granular disintegration of some of the capillary walls

FIG. D *Acute membranous glomerulonephritis* of eclampsia This firm appearing thickening of the basement membrane is more nearly the standard prototype of glomerular change occurring in eclampsia.




FIG. A. *Acute membranous glomerulonephritis of eclampsia* with glomerular ischemia, marked focal fibrinoid alteration of glomerular capillary walls, and thrombosis of the afferent arteriole and glomerular capillaries.

FIG. B. *Lower magnification* of kidney of figure A showing fibrinoid necrosis of basement membranes of glomerular capillaries, thrombosis of their lumens and hydropic hyaline droplet degeneration with actual necrosis of epithelium of proximal convoluted tubules.

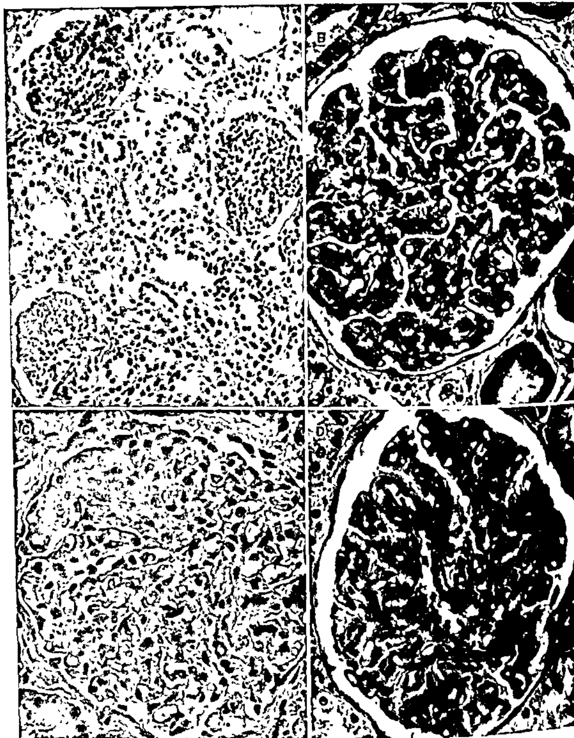



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PLATE 101. ACUTE GLOMERULONEPHRITIS IN ECLAMPSIA




FIG. A. *Acute membranous glomerulonephritis of eclampsia* with glomerular ischemia, marked focal fibrinoid alteration of glomerular capillary walls, and thrombosis of the afferent arteriole and glomerular capillaries.

FIG. B. *Lower magnification* of kidney of figure A showing fibrinoid necrosis of basement membranes of glomerular capillaries, thrombosis of their lumens and hydropic, hyaline droplet degeneration with actual necrosis of epithelium of proximal convoluted tubules.

# PLATE 100. Acute Glomerulonephritis in Eclampsia

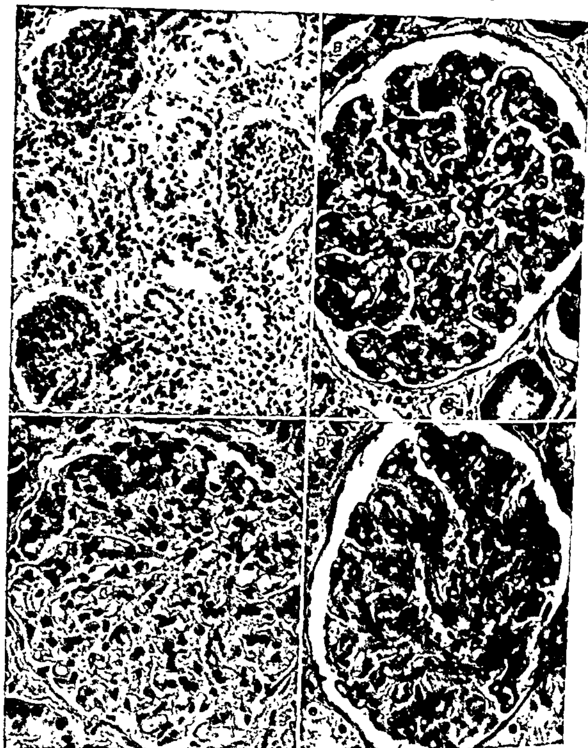



Fig. A *Acute proliferative glomerulonephritis* associated with clinical eclampsia. This patient was 16 years old and in her last month of pregnancy (A F I P Acc 100191)

Fig. C *Acute membranous glomerulonephritis* of eclampsia showing glomerular ischemia, decreased cellularity and membranous thickening of the capillary walls intermediate in quality between those of figure B and figure D

Fig. B *Acute membranous glomerulonephritis* of eclampsia with ischemia, and granular disintegration of some of the capillary walls

Fig. D *Acute membranous glomerulonephritis* of eclampsia. This firm appearing thickening of the basement membrane is more nearly the standard prototype of glomerular change occurring in eclampsia




FIG. A. *Acute membranous glomerulonephritis of eclampsia* with glomerular ischemia, marked focal fibrinoid alteration of glomerular capillary walls, and thrombosis of the afferent arteriole and glomerular capillaries

FIG. B. *Lower magnification* of kidney of figure A showing fibrinoid necrosis of basement membranes of glomerular capillaries, thrombosis of their lumens and hydropic, hyaline droplet degeneration with actual necrosis of epithelium of proximal convoluted tubules

is not of a significance to be reflected in the lowering of the total blood level The albuminuria rarely exceeds 0.2 to 0.3 per cent However, as much as 3 grams of protein have been excreted in 24 hours by presumably healthy young adults (Peters and Van Slyke) Obviously, such a finding calls for extreme care and judgment in ruling out organic renal disease The *urinary protein consists of serum* albumin as well as euglobulin, and the ratio of albumin to globulin (2 to 1) is considerably lower than it usually is in organic renal disease (Wallis), where it is of the order of 5–10 to 1.

*The albuminuria is often* constant but some cases show great irregularity in the periodicity of the albuminuria The albuminuria may not be the only finding in the urine, small numbers of hyaline and granular casts, and even a few red blood cells may be present. At the height of the proteinuria, there may be oliguria The standard tests for renal function, however, disclose no impairment

*Pathogenesis*

If proteinuria, which often is the first indication of severe renal disease, is of no harmful significance, then what is its mechanism? In many cases, probably in the great majority, the excessive release of protein into the urine is related to posture or lordosis Lordosis may affect a proteinuria by virtue of the position of the left renal vein which lies immediately anterior to the aorta, the right renal vein lies free of the aorta It is assumed that the lordosis, by increasing the convexity of the aorta, exerts a transmitted pressure on the compressible left renal vein in contact with its anterior surface. The resulting increased venous pressure results in proteinuria Occlusion of the renal vein is known to produce albuminuria and indeed, cases of the nephrotic syndrome have resulted from thrombotic occlusion of the main renal veins, as previously indicated Moreover, al*buminuria, from passive congestion secondary* to cardiac failure is a well recognized phenomenon In orthostatic albuminuria, the protein has been found to come from the left kidney only (Hinman), that is, the kidney of which the renal vein is likely to be compressed by lordosis.

Those instances of *benign albuminuria* that cannot be related to posture are difficult to explain. Focal infection has been considered responsible for the glomerular permeability in some cases, and for this reason a few observers advise that serious efforts be made to remove such foci, even the less overt ones. Undoubtedly, scattered examples of nonspecific focal glomerulonephritis may masquerade as benign or orthostatic albuminuria, but such instances are not numerous. The relationship of benign albuminuria to exercise, emotional reactions or exposure to cold suggests an increased glomerular permeability, due probably to sudden relative glomerular ischemia or glomerular stasis Marked but transitory albuminuria has occasionally followed the administration of vaccines, for example, yellow fever vaccines. The association of the proteinuria with growth and puberty is still to be explained.

*Diagnosis*

The importance of differentiating this "benign albuminuria," a term suggested by Fishberg, from the albuminuria secondary to organic renal disease is as obvious as it may be difficult The absence of hypertension, edema, appreciably abnormal urinary sediment, renal dysfunction as measured by standard tests, retinopathy, and of changes *in the level* of protein and other blood constituents, favors

Fig A *Acute membranous glomerulonephritis* of eclampsia (Mallory-Heidenhain stain)

Fig B *Lupus erythematosus-like lesion in* acute membranous glomerulonephritis of eclampsia

Fig C *Simulation of "wire-loops"* of disseminated lupus erythematosus is marked in this instance of acute membranous glomerulonephritis of eclampsia

Fig D *Liver in eclampsia* showing the characteristic periportal hemorrhage and necrosis, and thrombosis of sinusoids

Fig E *Residuum of eclampsia* at the age of 35 followed by persistent and progressively increasing hypertension *to 200/100 over the next 13 years The only significant renal change* is marked afferent arteriolosclerosis as shown here



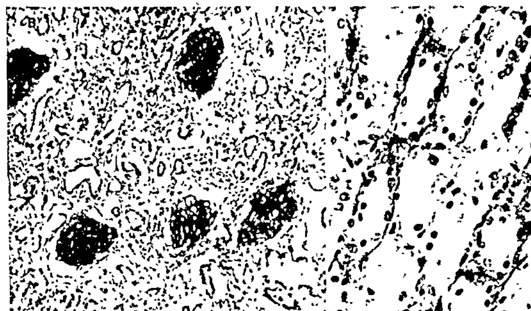




FIG. A. *Argyrosis of kidney.* Careful examination reveals black spots of impregnated glomeruli and pyramids darkened by deposits of silver.

FIG. B. *Glomerular argyrosis* from a patient who was treated with a solution of silver nitrate administered orally for a gastric ulcer.

FIG. C. *Argyrosis* with granules of silver adsorbed onto peritubular basement membranes.




FIG A *Argyrosis of basement membranes* of medullary tubules due to silver medication (unstained section)

FIG B *Glomerular argyrosis* due to silver medication. Glomerular (or tubular) argyrosis apparently effects remarkably little renal dysfunction.

FIG C *Normal argyrophilia of basement membranes* of glomerular capillaries and tubules as demonstrated by modified Bielschowsky's silver stain

he diagnosis of benign albuminuria Moreover, the relationship of albuminuria to posture s additional evidence of this condition, but it must be remembered that albuminuria secondary to organic renal lesions may be aggravated by postural changes However, in benign orthostatic albuminuria, ureteral catheterization reveals that the albumin comes only from the left kidney. Perhaps the most relevant diagnostic problem is the differentiation of benign albuminuria from chronic glomerulonephritis of the nephrotic type This differentiation may be made as a rule by the absence of edema, hypoproteinemia and hypercholesteremia, as well as the absence of birefringent lipid in the urine. Furthermore, the albuminuria leading to the nephrotic syndrome must be abundant and protracted, a situation that rarely is found in benign albuminuria.

*Prognosis*

Benign albuminuria eventually clears spontaneously, sometimes at puberty, at other times it may last as long as 30 years (Fox). There is no way to predict its duration Apparently, the albuminuria does not predispose an individual to organic renal disease Treatment of the albuminuria *per se* is generally not worthwhile, and may focus undue attention on an innocuous urinary finding .

REFERENCES

*Glomerulonephritis*


ADDIS, T Glomerular Nephritis New York, Macmillan, 1948

ALLEN, A C Medical Diseases of the Kidney Army Inst of Path Registry Press, 1947

——, AND SIROTA, J H Morphogenesis and significance of degenerative verrucal endocardiosis (terminal endocarditis, endocarditis simplex, nonbacterial thrombotic endocarditis) Am J Path 20: 1025–1056 1944

——, AND SPITZ, S A comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases Am J Path 21: 603–681, 1945

BAEHR, G Glomerular lesions of subacute bacterial endocarditis J Exper Med 15 330–347, 1912

BELL, E T Lipoid nephrosis Am J Path 5: 587–622, 1929

—— Glomerular lesions associated with endocarditis Am J Path 8: 639–661, 1932

—— The early stages of glomerulonephritis Am J Path 12. 801–824, 1936

—— Clinical and pathological study of subacute and chronic glomerulonephritis, including lipoid nephrosis Am J Path 14 691–736, 1938

BRADLEY, S E, AND TYSON, C J Medical Progress, "nephrotic syndrome" New England J Med 238. 223, 260, 1948

CANNADY, E W AND O'HARE, J P A critical survey of the retinal lesions in chronic glomerular nephritis J A M A 103. 6–10, 1934

CHRISTIAN, H A Classification of chronic nephritis J A M A 85. 1701–1702, 1925

DUNN, J S Fundamental lesion in acute diffuse intracapillary glomerulonephritis J Path and Bact 51. 169–188, 1940

DUVAL, C W, AND HIBBARD R J Experimental glomerulonephritis induced in rabbits with endotoxic principle of Streptococcus scarlatinae J Exper Med 44: 567–580, 1926

EDITORIAL Prevention of rheumatic fever and acute nephritis by early penicillin treatment of hemolytic streptococcus infections New England J Med 242: 1025–1028, 1950

ELLIS, A Natural history of Bright's disease, clinical, histological and experimental observations Lancet 1: 1–7, 1942

EMERSON, C P The pathogenesis of anemia in acute glomerulonephritis Estimations of blood production and blood destruction in a case receiving massive transfusions Blood 3: 363–372, 1948

FAHR, G AND KERKOF, A Plasma colloid osmotic pressure as a factor in edema formation and edema absorption Am J Physiol 116: 46, 1936

FAHR, TH Pathologische Anatomie des Morbus Brightii Handbuch der speziellen pathologischen Anatomie und Histologie Henke, F, and Lubarsch, O Berlin, J Springer, Vol 6, Pt 1, 1925, Vol 6, Pt 2, 1931

FISHBERG, A M Hypertension and Nephritis Philadelphia Lea and Febiger, 1939

GREENSPAN, S A, AND KRAKOWER, C A Direct evidence for the antigenicity of the glomeruli in the production of nephrotoxic serums Arch Path 49 291–297, 1950

HERBUT, P A Diffuse glomerulonephritis following revaccination for smallpox Am J Path 20: 1011–1021, 1944

HORN, H The experimental nephropathies Arch Path 23. 71, 241, 1937

——, KLEMPERER, P AND STEINBERG, M F Vascular phase of chronic diffuse glomerulonephritis Arch Int Med 70. 260–283, 1942

HARTZ, P H, VAN DER SAR, A, AND VAN MELTEREN, A Occurrence of mitotic divisions in glomeruli in glomerulonephritis and malignant sclerosis Am J Path 17: 563–570, 1941

JENSEN E J, BAGENSTOSS, A H, AND BARGEN, J A The kidney in chronic ulcerative colitis Proc Staff Meet Mayo Clinic 25. 244–251, 1950.




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——, AND SPITZ, S A comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases Am J Path 21, 603-681, 1945

BAEHR, G Glomerular lesions of subacute bacterial endocarditis J Exper Med 15: 330-347, 1912

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—— Glomerular lesions associated with endocarditis Am J Path 8. 639-664, 1932

—— The early stages of glomerulonephritis Am J Path 12: 801-824, 1936

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ELLIS, A Natural history of Bright's disease, clinical, histological and experimental observations Lancet 1 1-7, 1942

EMERSON, C P The pathogenesis of anemia in acute glomerulonephritis Estimations of blood production and blood destruction in a case receiving massive transfusions Blood 3 363-372, 1948

FAHR, G, AND KERKOF, A Plasma colloid osmotic pressure as a factor in edema formation and edema absorption Am J Physiol 116 46, 1936

FAHR, TH Pathologische Anatomie des Morbus Brightii Handbuch der speziellen pathologischen Anatomie und Histologie Henke, F, and Lubarsch, O Berlin, J Springer, Vol 6, Pt 1, 1925; Vol 6, Pt 2, 1934

FISHBERG, A M Hypertension and Nephritis Philadelphia, Lea and Febiger, 1939

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HORN, H The experimental nephropathies Arch Path 23. 71, 211, 1937

——, KLEMPERER, P, AND STEINBERG, M F Vascular phase of chronic diffuse glomerulonephritis Arch Int Med 70: 260-283, 1942

HARTZ, P H, VAN DER SAR, A, AND VAN MEETEREN, A Occurence of mitotic divisions in glomeruli in glomerulonephritis and malignant sclerosis Am J Path 17: 563-570, 1941

JENSEN, E J, BAGENSTOSS, A H, AND BARGEN, J A The kidney in chronic ulcerative colitis Proc Staff Meet Mayo Clinic 25: 244-251, 1950

KAY, C F The mechanism of a form of glomerulonephritis, nephrotoxic nephritis in rabbits Am J M Sc 204: 483–490, 1942

LADUE, J S Role of congestive heart failure in production of edema of acute glomerulonephritis Ann Int. Med 20: 405–422, 1944

LANDER, H. B Effects of measles on nephrotic syndrome Am J Dis Child 78: 813–815, 1949

LIBMAN, E The clinical features of cases of subacute bacterial endocarditis that have spontaneously become bacteria-free Am J M Sc 146: 625–645, 1913

LITTMAN, D, AND SCHAAF, R S Therapeutic experiences with subacute bacterial endocarditis with special reference to the failures New England J Med 243: 248–252, 1950

LOHLEIN, M Ueber hämorrhagische Nierenaffektionen bei chronische ulzeröser Endokarditis (*Embolische nichteiteriger Herdnephritis*) Med Klin 6: 374–379, 1910

LONGCOPE, W T The production of experimental nephritis by repeated proteid intoxication J. Exper Med 18: 678–703, 1913

—— The pathogenesis of glomerular nephritis Bull. Johns Hopkins Hosp 45: 335–360, 1929

LUKENS, F. D W, AND LONGCOPE, W T Experimental acute glomerulitis. J Exper Med 53: 511–526, 1931

MARGOLIS, G, FORBUS, W D, KERBY, G P, AND LIDE, T N Glomerulonephritis occurring in experimental brucellosis in dogs Am J Path 23: 983–993, 1947

MASUGI, M, AND SATO, Y Über die allergische Gewebsreaktion der Niere Zugleich ein experimentelle Beitrag zur Pathogenese der diffusen Glomerulonephritis und der Periarteritis nodosa Virchow's Arch f path Anat 293: 615–664, 1934

MORE, R H, AND WAUGH, D Diffuse glomerulonephritis produced in rabbits by massive injections of bovine serum gamma globulin J Exper. Med 89: 541–554, 1949

MORITZ, A R, AND HAYMAN, J M, JR. The disappearance of glomeruli in chronic kidney disease Am J Path. 10: 505–518, 1934

MUNK, F Nierenkrankungen 2nd ed Berlin, Wien, Urban and Schwartzenberg, 1925

PAGE, I H Production of nephritis in dogs by roentgen rays Am J M Sc 191. 251–256, 1936

RENNIE, J B The edematous syndrome of nephritis with special reference to prognosis Quart J Med 16: 21–31, 1947.

REUBI, F Hydronephrose et glomerulonephrite (étude experimentale) Schweiz med Wchnschr 76: 457–461, 1946

SCHWARZ, H, KOHN, J L., AND WEINER, S B Lipoid nephrosis, observations over a period of 20 years Am J Dis. Child 65: 355–363, 1943

SCHWENTKER, F F, AND COMPLOIER, F C The production of kidney antibodies by injection of homologous kidney plus bacterial toxins J Exper. Med. 70: 223–230, 1939

SELYE, H Textbook of Endocrinology. 2nd Ed. Montreal, Acta Endocrinologica, Inc, 1949.

SEEGAL, D, AND EARLE, D. P.: A consideration of certain biological differences between glomerulonephritis and rheumatic fever. Am. J M. Sc. 201: 528–539, 1941.

SMADEL, J E Experimental nephritis in rats induced by injection of anti-kidney serum I Preparation and immunological studies of nephrotoxin J Exper Med 64: 921–942, 1936

TOWNSEND, S R, MASSIE, E., AND LYONS, R H Studies on the anemia of chronic glomerulonephritis and its relationship to gastric acidity. Am J M Sc 194: 636–645, 1937.

VOLHARD, F Die doppelseitigen hämatogen Nierenkrankungen Handbuch d. inn Med Berlin, J. Springer, 1931, pp 1–1826.

—— AND FAHR, TH Die Brightische Nierenkrankheit, Klinik, Pathologie und Atlas Berlin, J Springer, 1914.

WARREN, J V., AND STEAD, E A, JR: The protein content of edema fluid in patients with acute glomerulonephritis Am J. M Sc 208: 618–622, 1944

WEINSTEIN, L, BACHRACH, L, AND BOYER, N. H.: Observations on the development of rheumatic fever and glomerulonephritis in cases of scarlet fever treated with penicillin New England J Med 242: 1002–1010, 1950

WHITEHILL, M R, LONGCOPE, W T., AND WILLIAMS, R The occurrence and significance of myocardial failure in acute hemorrhagic nephritis. Bull Johns Hopkins Hosp 64: 83–113, 1939

YAMPOLSKY, J, AND MULLINS, D F: Acute glomerular nephritis in an infant with congenital syphilis Am J Dis Child 69: 163–172, 1945.

*Lupus Erythematosus*

ALLEN, A C, AND SIROTA, J H: Morphogenesis and significance of degenerative verrucal endocardiosis (terminal endocarditis, endocarditis simplex, nonbacterial thrombotic endocarditis) Am J. Path 20. 1025–1056, 1944.

——, AND SPITZ, S A comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases Am J Path 21: 603–682, 1945.

ARONSON, S, AND WALLERSTEIN, L The protean nature of scleroderma, with a note on pulmonary changes New York State J Med 50: 2723–2726 1950

BAEHR, G. Renal complications of endocarditis Tr A Am Physicians 46: 87–95, 1931

BAEHR, G, AND POLLACK, A D. Disseminated lupus erythematosus and diffuse scleroderma J A M. A 134: 1169–1174, 1947

BANKS, B M: Is there a common denominator in scleroderma, dermatomyositis, disseminated lupus erythematosus, the Libman-Sacks syndrome, and polyarteritis nodosa? New England J Med 225: 433–444, 1941.

Bevans, M Pathology of scleroderma with special reference to the changes in the gastrointestinal tract. Am J Path 21:25–51, 1945

Gross, L The cardiac lesions in Libman-Sacks Disease with consideration of its relationship to acute diffuse lupus erythematosus Am J. Path 16:375–408, 1940

Hargraves, M M, Richmond, H, and Morton, R Presentation of two bone marrow elements, the "Tart" cell, and the "L E" cell Proc Staff Meet Mayo Clinic 23. 25–28, 1948

Haserik, J R, and Bortz, D W A new diagnostic test for acute lupus erythematosus Cleveland Clin Quart 16:158, 1949

——, and Sundberg, R D The bone marrow as a diagnostic aid in acute disseminated lupus erythematosus J Invest Dermat 11: 209, 1948

Karelitz, S, and Walt, S K Dermatomyositis Am J Dis Child 43. 1134–1149, 1932

Kinney, T D, and Maher, M M Dermatomyositis, a study of five cases Am J Path 16. 561–594, 1940

Klemperer, P, Pollack, A D, and Baehr, G Pathology of acute lupus erythematosus Arch Path 32: 569–631, 1941

Klingman, W O Dermatoneuromyositis resulting in scleroderma Arch Neurol & Psychiat 24: 1187–1198, 1930

Krupp, M A Urinary sediment in visceral angiitis (periarteritis nodosa, lupus erythematosus, Libman-Sacks "disease"), quantitative studies Arch Int Med 71 54–61, 1943

Langmead, F S The relationship between certain rare diseases—generalized scleroderma, calcinosis, dermatomyositis, myositis fibrosa. Arch Pediat 40: 112–120, 1923

Libman, E Characterization of various forms of endocarditis J A M A 80 813–818, 1923

——, and Sacks, B A hitherto undescribed form of valvular and mural endocarditis Arch Int Med 33 701–737, 1924

Masugi, M and Ya, S Die diffuse Sclerodermie und ihre Gefassveränderung Virchow's Arch f path Anat 302: 39–62, 1938

Matsui, S Über die Pathologie und Pathogenese von Sclerodermia universalis Mitt a d med Fak d k Univ Tokyo 31: 55–116, 1924

Rake, G On the pathology and pathogenesis of scleroderma Bull Johns Hopkins Hosp 48: 212–227, 1931.

Spain, D M, and Thomas, A G The pulmonary manifestations of scleroderma An anatomic-physiological correlation Ann Int Med 32: 152–161, 1950

Talbott, J H, Gall, E A, Consolazio, W V, and Coombs, F S Dermatomyositis with scleroderma, calcinosis, and renal endarteritis associated with focal cortical necrosis Arch Int Med 63: 476–496, 1939

Walker, S A, and Benditt, E P The serum proteins in diseases of connective tissue J Invest Dermat 14: 113–120, 1950

Wolf, A, and Wilens, S L Dermatomyositis, a report of two cases with complete autopsy Am J Path 12: 235–248, 1936

*Toxemias of Pregnancy*

Bell, E T Renal lesions in toxemias of pregnancy. Am J Path 8: 1–42, 1932

Boyd, E M Blood Lipids in eclampsia Am J Obs & Gynec 30: 323–332, 1935

Corwin, J, and Herrick, W W Toxemias of pregnancy in relation to chronic cardiovascular and renal disease Am J Obst & Gynec 14: 783–796, 1927

Dexter, L, Weiss, S, and others Preeclamptic and Eclamptic Toxemia of Pregnancy Boston, Little, Brown, 1941

——, ——, Haynes, F W, and Sise, H S Hypertensive toxemia of pregnancy J A M A 122: 145–152, 1943

Dieckmann, W J The Toxemias of Pregnancy. St Louis, C V Mosby, 1941

——, and Brown, I Do eclampsia and pre eclampsia cause permanent vascular renal pathology? Am J Obst & Gynec 37 762–776, 1939

Fahr, Th Die pathologisch-anatomischen Veranderungen der Niere und Leber bei der Eklampsie, in Hinselman, H, Die Eklampsie Bonn, F Cohen, 1924

Fink, K Ursachen u Bedeutung des Hydrops bei schwangeren Frauen Ztschr f Geburtsh u Gynäk 84: 1–33, 1921

Herrick, W W, and Tillman, A J B Toxemia of pregnancy its relation to cardiovascular and renal disease, clinical and necropsy observations with a long follow-up Arch Int Med 55. 643–664, 1935

Hofbauer, J Pregnancy changes in the uterine cervical ganglia (Frankhäuser) as causative factors of vascular hypertension in toxemia. Am J Obst & Gynec 59: 1383–1388, 1950

Löhlein, M Zur pathogenese der Nierenkrankheiten Nephritis, Nephrose, mit besonder Berücksichtigung der Nephropathia gravidarum Deutsche med Wchnschr 44 1187–1189, 1918

Page, E W Relation between hydatid moles, relative ischemia of the gravid uterus, and the placental origin of eclampsia Am J Obst & Gynec 37: 291–293, 1939

Peckham, C H Time of onset and duration of toxemias of late pregnancy in relation to the development of permanent vascular damage Am J Obst & Gynec 42: 638–645, 1941

[illegible]

Schroeder, H A, and Goldman, M L Test for the presence of "hypertensive diencephalic syndrome" Am J Med 6: 162–167, 1949

SEITZ, L Zur Symptomatologie, Prophylaxe, und Therapie der Eklampsie und ihrer Vorstufen Arch f Gynak **142:** 52-73, 1930

SELYE, H. *The Physiology and Pathology of Exposure to Stress* Montreal, Acta Endocrinologica, Inc, 1950

STANDER, H J An analysis of 801 cases of toxemias of pregnancy New England J Med **201:** 458-466, 1929

TEEL, H M, AND REID, D E Eclampsia and its sequelae, a clinical follow-up of all cases at the Boston Lying-In Hospital over a 20 year period Am J Obst & Gynec **34:** 12-25, 1937.

*Functional Glomerular Permeability*

FISHBERG, A M Hypertension and Nephritis Philadelphia, Lea and Febiger, 1939

FOX, R. H · Adolescent albuminuria in relation to life assurance Lancet **1:** 116-118, 1921

HINMAN, F. The Principles and Practice of Urology *Philadelphia, Saunders, 1935*

LEUBE, W Ueber die Ausscheidung von Eiweiss in Harn des gesunden Menschen. Virchow's Arch f path Anat **72:** 145-157, 1878

MACLEAN, H. The incidence of albuminuria and casts in British soldiers during training and the relationship of this condition to war nephritis Brit M J **1:** 94-98, 1919

PETERS, J. P, AND VAN SLYKE, D D Quantitative Clinical Chemistry. Baltimore, Williams and Wilkins, 1931, p 708.

WALLIS, R L M : Non-nephritic albuminuria Proc. Roy. Soc Med **13:** 96-104, 1920.

# 7. Diseases of the Tubules

**Classification of Diseases of the Tubules**

- Proximal nephron nephrosis
  - Osmotic
  - Hyaline granule
  - Fat
  - Mercury
  - Potassium dichromate
  - Potassium chlorate
  - Ethylene glycol
  - Diethylene glycol
  - Bismuth
  - Hemosiderosis
    - Marchiafava-Micheli syndrome
    - Favism
    - *March hemoglobinuria*
    - Cold hemoglobinuria
- Proximal and distal nephron nephrosis
  - Hemoglobinuric ("lower nephron") nephrosis
  - Cholemic
  - Hydroquinone-pyrogallic acid
  - Sulfonamide
  - von Gierke's disease
- Distal nephron nephrosis
  - Myeloma
  - Gout
  - Uric acid "infarct"
  - "Inclusion Disease"
- Parenchymal nephrocalcinosis

## Osmotic Nephrosis*

In the years around 1910, hypertonic (50 per cent) sucrose, the disaccharide of glucose and fructose, was used extensively to combat cerebral or generalized edema (Jackson et al, Murphy et al). However, its use was soon appreciably discouraged by the publication of reports of rather striking swelling of the renal tubular epithelium produced by the sucrose (Lindberg, Anderson). The histologic change in the epithelium was so prominent that the equivocal nature or complete lack of evidence of renal dysfunction with moderate doses at proper intervals was generally disregarded. Actually, most of these data were available in 1906 (Lamy et al) and re-emphasized in 1933 when Helmholz reported the effects of hypertonic sucrose in rabbits and in one human case. He subsequently observed rather similar qualitative changes with hypertonic glucose, sorbitol, sodium sulfate and urea. Phenolsulfonphthalein excretion is diminished in rabbits given excessive doses of sucrose at relatively close intervals (Helmholz). However, these rabbits, weighing only 4 to 8 pounds received as much sucrose as would be given therapeutically to an adult weighing about 150 pounds. The overall evidence is that the administration of sucrose in proper doses, in the absence of severe dehydration, is a safe procedure as far as renal function is concerned.

### *Histologic Appearance*

The lesions produced by hypertonic sucrose (osmotic nephrosis) are confined almost exclusively to the proximal portion of the nephron including the descending limb of the loop of Henle. The lesion consists of a bland swelling of the epithelium by a sieve-like trellis of vacuoles, diffusely and regularly distributed throughout the cells favoring no one portion of the cell over any other. If only a single, extensively involved cell were examined, the vacuolization would be indistinguishable from that produced by diffusely dispersed lipid as in the nephrotic phase of chronic glomerulonephritis, that is, lobular or membranous glomerulonephritis. With special stains, it is discovered that these vacuoles contain neither fat nor glycogen, but are *hydropic*, in other words, they contain at least no stainable constituent. In routine

* Some writers object to the use of *nephrosis* on the ground that the suffix "osis" means "abundance of," and therefore suggest the substitution of "nephropathy" for "nephrosis." It is not especially clear why the words osmosis, thrombosis and psychosis are not found just as inadequate. In point of fact, "osis," as has been indicated previously (Am J Path 20: 1040, 1944), signifies either "an abnormal or diseased condition" *or* "a physiological increase" (Webster's International Dictionary, Second Edition, unabridged). Hence, "nephrosis" means disease of the kidney. By virtue of long usage, rather than literal definition, it has come to indicate *tubular* disease. The term "tubular nephritis" is attractive and has many advocates but it has the disadvantages of inaccuracy in its application to noninflammatory tubular lesions, and of some unwieldiness when the etiologic agent is appended.

sections, the *diffuseness* of the lesion throughout an individual proximal part of a nephron suggests the diagnosis of hydropic rather than lipid vacuolization This is *especially true if*, in addition, most of the nephrons are involved, as they frequently are (plate 106) Despite the most conspicuous vacuolization, the brush border of the cells is usually intact Often, beneath the cilia, the *cytoplasm is least* "vacuolated" and there may be a rim of hyaline granules as if displaced to the luminal border of the cell.

Actually, when studied under high magnification, the spaces that are loosely called "vacuoles" appear to represent collections of intracytoplasmic fluid that have been collected into the cell and have separated the normal granules so as to simulate vacuoles (plate 106 B) The impression that these are true vacuoles surrounded by a membrane in the morphologic sense of contractile vacuoles of paramecia or even of a lipid vacuole is, therefore, not substantiated by detailed histologic examination. The cytologic details are more in harmony with the conviction that the fluid, imbibed by the cell subjected to the hypertonic sucrose, elbows apart the ordinary cytoplasmic acidophilic granules readily visible in compact form in normal epithelium of proximal tubules These lesions, with rare exceptions (plate 106 B) are entirely reversible

The lumens of the proximal tubules may appear appreciably narrowed in cases with the more conspicuous lesions However, Bowman's spaces are not significantly dilated and it is questioned if this apparent histologic compromise of the tubular lumen by the swollen tubular cells is of physiologic significance This epithelial swelling begins about an hour after the *hypertonic sucrose is administered, reaches its* maximum in 48 hours, and disappears in about 15 days (Helmholz).

It is of interest to note that loops of distal *convoluted tubules in immediate* juxtaposition to severely involved proximal tubules usually show no change. Occasionally, mild vacuolization in these distal tubules is seen, but may be easily overlooked because of the sharp quan*titative contrast to the change in the proximal* tubules.

Hypertonic sucrose may similarly alter the parietal epithelium of Bowman's capsule but otherwise does not affect the glomeruli, vessels, *or interstitium of the normal kidney Its effect* on the interstitial edema of the kidney has not been satisfactorily demonstrated

*Other Modes of Production of Osmotic Nephrosis*

This same type of vacuolization may be produced by other sugars in hypertonic solutions, such as 50 per cent xylose and 20 per cent inulin (plate 109, 110). We have noted it also with a variety of other hypertonic solutions, including 30 per cent acacia and 15 per cent creatinine, with subcutaneous and intraperitoneal injections of 50 per cent sucrose, and with the intravenous inoculation of 50 per cent sucrose as well as 50 per cent glucose in phloridzinized animals (plate 110 A). Moreover, we have observed the vacuoles after large amounts of isotonic sucrose had been administered intravenously Wilmer, too, found that the epithelial vacuolization in rabbits produced by the intraperitoneal or subcutaneous injection of sucrose was not prevented by phloridzin *He made the* interesting observation that intraperitoneal hypertonic (50 per cent) sucrose resulted in the vacuolar change in the pregnant rat but not in the fetus We have, however, observed this *type of vacuolization in* the kidneys of newborn

Fig A *Osmotic nephrosis* (produced by 150 cc of 50 per cent sucrose solution given intravenously over a three day period) characterized by reversible vacuolated, hydropic swelling of epithelium principally of proximal convoluted tubules Hyaline droplets are present in many tubules and represents intrinsic alteration of epithelial cytoplasm rather than absorbed protein

Fig B *Changes identical with sucrose nephrosis* can be caused by other hypertonic solutions including 10 per cent dextrose as in this case The epithelial degeneration present in one tubule in above photograph is uncommon (Fat and glycogen stains are negative )

Fig C. *Changes of the sucrose type of nephrosis* were produced in this kidney from a 7 day old infant by 14½ ounces of 5 per cent glucose given orally and an infusion of 30 cc of 5 per cent glucose




(Legends on facing page.)

infants (plate 110 D) Intraperitoneal injection of hypertonic sucrose in the aglomerular toadfish does not produce the tubular change (Wilmer) Ligation of the ureter does not prevent the formation of sucrose vacuolization, in contrast to the protection afforded against poisoning by mercury bichloride and uranium nitrate by ureteral ligation Hayman and Hartman observed transient hyperlipemia in animals after the administration of hypertonic sucrose Incidentally, the coarse large irregular type of hydropic vacuolization of the proximal tubular epithelium found occasionally in dysentery (Jaffé and Sternberg), cholemic nephrosis and ulcerative colitis (Jensen, et al, Kulka et al) (plate 108 B) is morphologically distinguishable from that of osmotic nephrosis

*Physiologic Pathology*

The interpretation of these facts is that many compounds may produce a hydropic vacuolization of the proximal tubular epithelium if they are present in sufficient molar concentration in the lumen in this part of the nephron Hence, the term "osmotic nephrosis" is suggested. It is our belief that the intracytoplasmic "vacuoles" are the direct result of the disturbance in the normal oncotic relationships between the osmotic pressure of the tubular fluid and that of the fluid within the tubular epithelial cytoplasm Hypertonic sucrose disturbs this relationship and causes the cellular imbibition of fluid so as to separate the cellular granules into "vacuolar compartments" Sucrose happens to be a particularly effective agent for the production of osmotic nephrosis because, unlike glucose, it is not metabolized and is excreted practically quantitatively within a short time, thereby exerting its maximal osmotic effect

Even though glucose is metabolized, if a sufficient concentration of it is delivered to the tubular lumens by means of infusions or abnormal metabolism, as in a patient with diabetes mellitus, osmotic nephrosis will result. And, to be sure, such vacuolization is commonly seen in diabetic patients and is misinterpreted as glycogenic vacuolization. The failure of these vacuoles to take the stain for glycogen is generally ignored and attributed to the type of fixative used, or, no special stain is done, and the hydropic vacuoles are dogmatically labeled glycogen notwithstanding the fact that glycogen vacuoles in diabetes mellitus occur not in the convoluted portion of the proximal tubules but characteristically in the loops of Henle Similarly, and just as erroneously, the vacuoles that follow the administration of acacia or gelatin are usually considered to be actual collections of these substances in the proximal tubular epithelium, whereas, they too are hydropic vacuoles of osmotic nephrosis. This vacuolization, incidentally, appears responsible for the gross renal enlargement observed after the administration of gelatin (Baxter and Cotzias).

*Physiologic Implications of Osmotic Nephrosis*

The detail with which osmotic nephrosis has been outlined reflects the author's conviction that the phenomenon is of importance, not be-

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Fig A *Osmotic (sucrose) nephrosis* in milder form These vacuoles do not take the stain for fat or glycogen

Fig B *Osmotic nephrosis Changes produced by infusions* of 10 per cent glucose Negative for glycogen and fat The brush border helps to identify the tubule as belonging to the proximal nephron

Fig C *Osmotic nephrosis in a diabetic Epithelial changes similar to those of sucrose nephrosis* These are hydropic changes apparently effected by osmotic relationships between lumen and tubular cells Such lesions in diabetics are often erroneously dismissed as due to deposits of glycogen

Fig D *Osmotic nephrosis Hydropic vacuolization in proximal tubules in cholera* identical with those of sucrose nephrosis and probably dependent on oncotic changes associated with severe diarrhea This vacuolization is different from the coarse type also found in dysentery (Jaffé and Sternberg) and in ulcerative colitis (plate 108, figure B)

Fig E *Fat nephrosis Phosphorus poisoning* with marked fatty vacuolization of epithelium of proximal convoluted tubules This may be distinguished from the lesion of sucrose or oncotic nephrosis even in routine sections stained with hematoxylin-eosin

Fig F *Fat nephrosis in proximal tubules in diabetes mellitus.* This basal vacuolization is easily recognized as lipid even in such routine sections A similar lesion occurs in other conditions, as in hepatitis due to carbon tetrachloride or chloroform




(Legends on facing page)

cause of any impairment of renal function wrought by hypertonic solutions, but because of the normal physiologic implications It is an importance inferred from the impression that if we knew the exact cytomechanics of the epithelial vacuolization, *we should then have some* information about normal renal function, and, undoubtedly, information, too, about vacuolization of cells in other tissues. In this latter regard, there is supporting evidence from Opie's experimental production, in vitro, of vacuolization of renal tubular epithelium placed in hypotonic solutions. The vacuolization simulates the sucrose lesions histologically In other words, it appears that renal vacuolization is produced not by the presence of sucrose or other administered substances within the cell in the sense of lipid or glycogen vacuoles, but by the imbibition of fluid within the renal epithelial cells by virtue of the oncotic changes produced by sucrose, glucose, *and even protein*, in *extravagant concentrations within the tubular* lumens and/or capillaries The fact that the solutions in Opie's experiments were *hypotonic* does not negate the thesis that these tubular epithelial changes are the result of osmotic influences The difference is one of site of action rather than mechanism

It is a reasonable premise, with the data at hand, that the mechanism of vacuolization due to hypertonic sucrose is essentially the same as that produced by other sugars Inasmuch as the sucrose is eliminated practically quantitatively within 24 hours (Keith et al.) and inasmuch as the vacuolization persists for several days thereafter, it is obvious that the vacuolization can hardly be the result of sucrose retention in the cells

Second, it is generally conceded that phloridzin prevents the reabsorption of glucose by the renal tubules and a similar barrier appears to *be effected against sucrose reabsorption. This* conclusion is confirmed by the identical clearance of glucose and sucrose (and xylose) in phloridzinized dogs (Smith) Nevertheless, the osmotic nephrosis, or tubular epithelial vacuolization, occurs following the intravenous administration of hypertonic glucose or hypertonic sucrose in phloridzinized animals Hence, the vacuolization is not the result of the intraepithelial accumulation of these hypertonic sugars which must exert their oncotic effects *from a position outside the tubular cell, most* likely the tubular lumen or possibly the peritubular capillaries.

Third, if the vacuolar lesions are dependent on an abnormally high concentration and effective osmotic pressure of a substance within the tubular lumens, why are the lesions more severe with 100 cc. of 50 per cent sucrose than with 100 cc. of 50 per cent glucose? As indicated, the reason is that the tendency of glucose to produce the lesion is appreciably neutralized by the *facts that (1) much of the glucose is metabo*lized and hence not available to exert osmotic suction in the tubular lumen, and (2) the glucose, in much greater proportion than sucrose, is reabsorbed across the tubular epithelium, thereby accounting for the loss of an additional increment in the osmotic tension within *the* tubular lumen Similarly, the reabsorption of 25 per cent xylose reduces the vacuologenic efficiency of xylose. The greater vacuolar effect

FIG A *Fatty changes in proximal tubules* in chronic membranous glomerulonephritis ("lipoid nephrosis") This diffuse distribution of lipid may be difficult or impossible to differentiate from osmotic nephrosis in routine sections

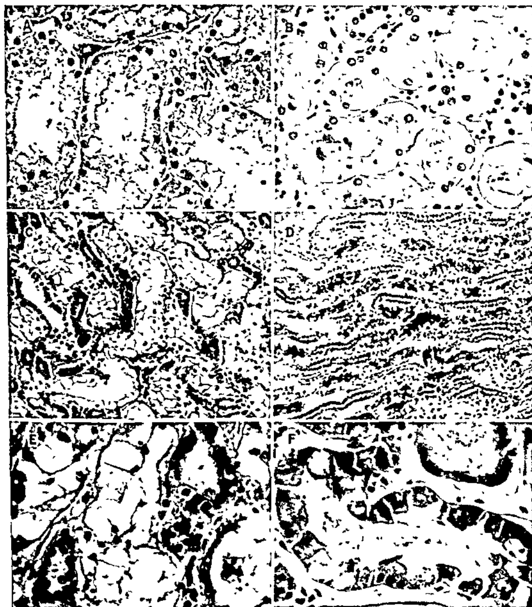
FIG B *Gross vacuolization* of the epithelium of the proximal nephron from a case of colonic carcinoma with diarrhea Similar changes are noted in cases of ulcerative colitis and occasionally in cholemic nephrosis Observed in 1918 by Jaffé and Sternberg

FIGS C AND D *Glycogen vacuoles (Armanni-Ebstein)* in loops and limbs of Henle in severe diabetes mellitus Figure D shows the positive stain for glycogen (black masses) in the vacuoles (Best's carmine )

FIG. E *Diethylene glycol nephrosis* with a destructive clear vacuolization The entire contents of many of these cells are cast off into the lumens. These vacuoles do not take the stain for fat or glycogen

FIG F. *Cholemic nephrosis* with a distinctive

## PLATE 108. NEPHROSIS OF PROXIMAL NEPHRON: OSMOTIC NEPHROSIS (DIFFERENTIAL DIAGNOSIS)




(Legends on facing page.)

of sucrose as opposed to the equally nonmetabolized inulin, is accounted for by the enormously greater molecular weight of the latter (about 5000 for inulin versus 342 for sucrose) and hence the much lower osmotic pressure of inulin

The conclusion therefore, is that the "vacuolar" lesion is produced by excessive concentration of sucrose, glucose, or, indeed, one of a great variety of substances, including urea, and sodium sulfate, within the proximal tubular lumen, and that this concentration results in imbibition of fluid, possibly from peritubular capillaries, into the epithelial cell with resultant temporary swelling Moreover, it is clear that the abnormal tubular concentration for each substance need not be obtained by the intravenous injection of a *hypertonic* solution The production of sucrose lesions by the intravenous injection of isotonic sucrose, the intraperitoneal and subcutaneous injections of hypertonic sucrose in rabbits (plate 110 B) and guinea pigs, as well as the injection of hypertonic sucrose into the lymph sacs of frogs, substantiates this point of view In each of these instances, the sucrose is necessarily absorbed into the blood stream in isotonic concentrations Therefore, the data focus again on the abnormally high concentration of the sucrose in the *tubular fluid*, rather than on its hypertonicity in the blood, as a cause of the epithelial swelling To explain why this same type of vacuolization is not produced in the lower portions of the nephron, as in the collecting tubules, one must resort to the teleologic explanation that renal epithelium in this region is "accustomed" to hypertonic solutions What actually enables these cells to withstand the oncotic pressure to which their more proximal counterparts are vulnerable is still to be learned From the structural point of view, the cells of the proximal tubules, by virtue of their normal rodlets and fine, loose granules, in contrast to the cytoplasm of the more distal tubules, seem especially vulnerable to this type of change.

### Hyaline Granule (Colloid Droplet) Nephrosis

*Relationship to proteinuria*

Although most observers assume that the glomerular filtrate is truly an ultrafiltrate of the plasma, and, therefore, protein-free, there are others—and their numbers *are increasing*—(e g , Addis, Oliver) who believe that normally during the course of the day, a *minute amount* of protein escapes into the glomerular filtrate and is then reabsorbed by the tubular epithelium Actually this hypothesis is inferential and is not supported by the determination of the protein content made by the original direct measurements on aspirated glomerular filtrate (Wearn and Richards, Richards). It is effectively pointed out, however, that proteins seep through other capillaries, and that microchemical methods do not permit detection of less than 0 020 Gm. per cent of protein, which is assumed to be the order of seepage, and finally that if this amount did escape the glomerular capillaries, there would have to result an albuminuria of about 36 Gm per day, instead of a normal of about 10 mg (Addis). Therefore, practically all of the 36 Gm of protein must be reabsorbed by tubular epithelium

A significant part of the evidence for the capacity of the tubules to reabsorb protein is considered to be the hyaline granules found in clear cases of proteinuria These granules are regarded as reabsorbed protein on evidence that is not altogether convincing. For a long time they were so regarded merely because they were associated with proteinuria, although some observers (Terbruggen) suggested that the granules consisted of protein in the process of being secreted into the tubular lumen by the epithelium. More recently, various proteins that had been coupled with red dye (disodium salt of 2-naphthol-3,3-disulfonic acid) were injected into animals, and colored granules were subsequently found in the proximal tubular epithelium (Smetana). It was therefore assumed that the colored intracytoplasmic granules represented the original protein, still coupled with dye, which was reabsorbed into the epithelium from the tubular lumen This is a key assumption which lacks adequate proof. Similar colored "droplets" were noted when the proteins and dyes were injected *separately* (Oliver) Moreover, droplets of hemoglobin are said to have been noted in the proximal tubular epithelium (Rather*). The reabsorption of hemoglobin comprises an especially complicated situation made more complicated by the well

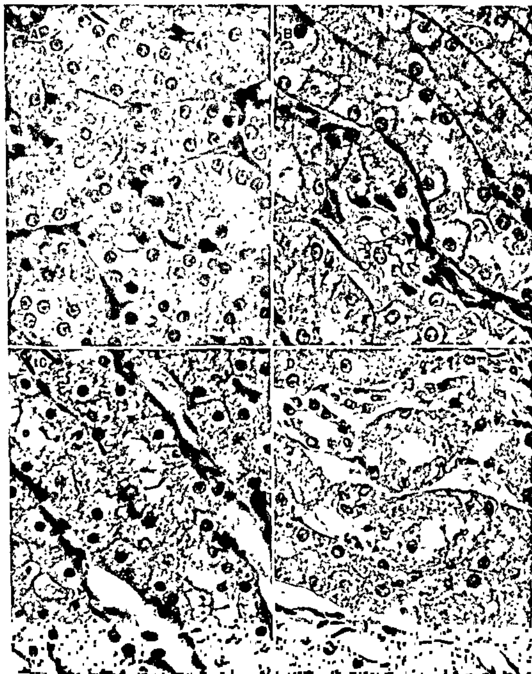



FIG A *Control kidney from normal rabbit*

FIGS B, C AND D illustrate osmotic nephrosis in rabbit given intravenous hypertonic injection of solutions of inulin (B), xylose (C) and urea (D)

known unreliability of the stains for hemoglobin in tissue, and by the presence of hemosiderin. It is of interest that in human cases of hemoglobinuric or myohemoglobinuric nephrosis, and after excretion of myohemoglobin in animals (Yuile, Gold and Hinds), droplets of hemoglobin are not observed in the proximal tubular epithelium.

*Intraepithelial origin of hyaline granules*

Nevertheless the evidence appears to us in favor of the view that the hyaline or colloid droplets, which are commonly seen in many renal diseases [such as, membranous or lobular glomerulonephritis ("lipoid nephrosis"), amyloidosis, malignant nephrosclerosis, and in instances of frank tubular degeneration from chemical poisons] are the result of an intrinsic intraepithelial alteration of the normal cytoplasmic granules This subject and point of view were convincingly and authoritatively presented in 1914 by Volhard and Fahr They concluded that these granules were evidence of cellular degeneration and that they were derived from normal cytoplasmic constituents which others had previously believed were the basilar Altman's granules. The observation of the various grades of severity of hyaline granular degeneration, from that in "lipoid nephrosis" to the extreme degree in necrotizing nephroses of potassium dichromate or diethylene glycol, makes no conclusion tenable other than that these acidophilic droplets constitute intracellular transformations of cytoplasmic structures rather than reabsorbed protein (plates 111, 112)

The original structures are the normal, fine, acidophilic granules and their underlying basilar rodlets The droplets may be huge, especially at the luminal border, where they may be seen in the process of extrusion rather than in athrocytosis The large extruded droplets are also found in the lumens of the tubules into which they have been sloughed; the large size of many of the granules makes their absorption by epithelial cells inconceivable. Moreover, the presence of these same granules in the parietal epithelial cells of Bowman's capsule (plate 112 D) *can hardly be construed to* indicate their origin from reabsorbed protein, since no one would consider reabsorption of protein a function of these cells It is pertinent that vital dye (trypan blue) *injected by itself* may also be found in the epithelium of Bowman's space (Suzuki) as well as in the epithelium of the proximal tubules

*Pathogenesis*

What is the mechanism of the formation of these granules? In 1947, it was suggested (Allen) that the original granules of the cells of the proximal convoluted tubules become swollen because of local changes in osmotic pressure, so that fluid is imbibed by the granules This explanation was based on the observation of these droplets in the proximal tubular cells after the administration of a variety of hypertonic solutions. Recently, Opie (1947) in a series of experiments, has produced similar changes in tubular epithelium of thin slices of kidney placed in hypotonic solutions and in distilled water He estimates (Opie, 1950) that, in potassium chromate nephrosis, for example, the osmotic pressure of the epithelial cells falls to that of the surrounding medium and returns to the normal level with recovery. This kind of observation, which appears to have been neglected by those who believe the granules represent reabsorbed protein masses, is additional strong evidence for the oncotic origin of the hyaline or colloid droplets of the tubular epithelium The fact that the number and size of granules decrease with increase in molecular weight of the protein (Oliver) further suggests *the oncotic basis for their formation* inasmuch as larger molecules exert less osmotic pressure than smaller ones The observation that the droplets become colored by dye even when the dye and protein are given separately is interpreted by us to mean the dye colors the epithelial cytoplasm including the oncotically enlarged granules It would seem altogether without basis to assume that the dye *especially selected* the droplets of "reabsorbed" protein. Moreover, the persistence of the colored granules in the renal epithelium for several weeks is not evidence that they represent reabsorbed protein inasmuch as Suzuki long ago (1912) *showed that the dye administered by itself may* be found as granules in the renal epithelium

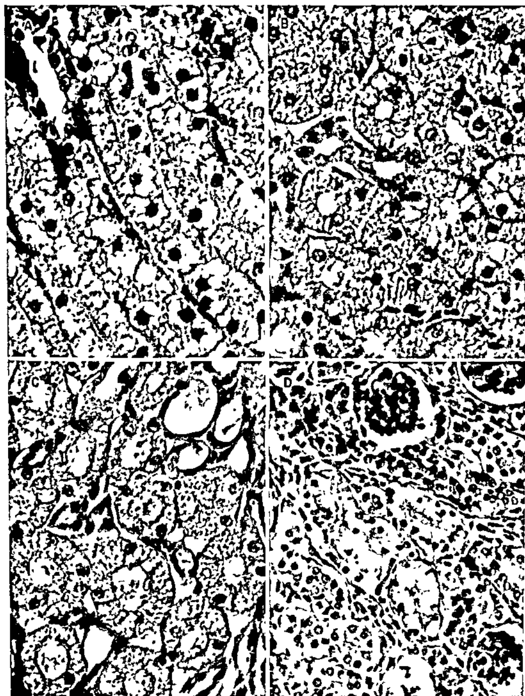



FIG A *Osmotic nephrosis* in rabbit from hypertonic sucrose (30 cc , 50 per cent intravenously) and phlorizin

FIG C *Osmotic nephrosis* in rabbit from hypertonic solution of sodium sulfate (10 cc , 20 per cent, intravenously, sacrificed in 15 hours)

FIG B *Osmotic nephrosis* in rabbit from the subcutaneous injection of hypertonic sucrose

FIG D *Osmotic nephrosis* in stillborn infant

three to four weeks later In addition, it is known that the proteins hemoglobin (as opposed to hemosiderin) and myohemoglobin quickly disappear from the kidney after reabsorption (Yule, 1941), within days—not weeks.

Finally, if the hyaline droplets did in fact represent reabsorbed protein, it might be reasonably anticipated that there would be a positive correlation between the occurrence of such droplets and the presence of proteinuria. No such correlation exists (Rather[5])

*Functional Disturbance from Hyaline Droplet Nephrosis*

It is stated that the hyaline droplets occur only in structurally undamaged epithelial cells inasmuch as they are not formed in regenerating epithelium, or in epithelium previously injured with uranium nitrate or bichloride of mercury (Oliver) On this basis, it has been concluded that the droplets "are not evidence of damage but proof of a certain functional and structural intactness" (Oliver).

It is entirely agreed that some vitality of the epithelial cell is essential for the appearance of the hyaline droplets This is not so because the integrity of the cell is necessary for the reabsorption of protein, but rather because a necrotic cell, perhaps *with ruptured cell membranes*, is not capable of the osmotic reactions of the intact cell. Similarly, a regenerating cell of the proximal tubule is structurally and chemically (e g , phosphatase content) a great deal different from the normal cell, and may appear as dissimilar from a cell of the proximal tubules as from a cell of the collecting tubules It is for these reasons that hyaline droplets do not tend to form in previously severely altered cells On the other hand, hyaline droplets usually represent a mild, reversible, osmotic reaction, but may constitute the initial phase of a necrotizing process *The evidence for this statement* may be observed, for example, in the various stages of degeneration of renal epithelium poisoned with potassium dichromate or diethylene glycol (plates 115, 119) Indeed, as already stated, Opie observed such granules in the epithelium of tubules exposed to dichromate, and concluded that there had been a marked reduction in the osmotic pressure of the epithelial cells In other words, osmotic changes, in special instances, can be carried out to irreversible proportions, causing cellular rupture and death.

In summary, the hyaline droplets represent a variety of osmotic nephrosis. This is not to deny that protein is reabsorbed by the tubules It is *merely that the reabsorbed protein does* not take the form of hyaline particles engulfed by the tubular epithelium from the glomerular filtrate.

## Fat Nephrosis

The term *fat nephrosis* is used in contradistinction to *lipoid nephrosis*, to refer to the prominence of lipid in the epithelium of the proximal convoluted tubules in patients who do not have the nephrotic syndrome. Lipoid nephrosis has for a long time designated the clinical and histologic entities that are herein regarded as forms of glomerulonephritis *with* edema It is felt that the *clinically silent*, reversible, *purely tubular*, histologic entity of fat nephrosis ought to be distinguished from lipoid nephrosis despite the use of possibly confusing terminology.

The histologic picture of fat nephrosis occurs in cases of phosphorus poisoning, in some cases of poisoning by carbon tetrachloride, chloroform, tetrachlorethane, chloral hydrate, bromoform, iodoform and in some cases of diabetes with hypercholesterolemia (plate 107). In the latter instance, there is usually evidence of severe *diabetes as well; in phosphorus* poison-

Fig A *Hyaline granules* with great diversity of size in proximal convoluted tubules in a case of malignant nephrosclerosis These "colloid droplets" result from swelling of intrinsic cytoplasmic granules rather than from reabsorbed protein

Fig B *Hyaline granules* in proximal convoluted tubules in case of sulfathiazole glomerulonephritis These cells are obviously in various stages of degeneration

Fig C *Hyaline granules* in epithelium of proximal convoluted tubules in malignant nephrosclerosis

PLATE 111. NEPHROSIS OF PROXIMAL NEPHRON: HYALINE (COLLOID) GRANULE NEPHROSIS




(Legends on facing page)

ing, there is generally equally prominent histologic evidence of fat in the liver, in the case of the volatile poisons, there is no direct correlation between the amount of fat in the liver and in the kidney.

The renal lesion is characterized by more or less of a coalescence of basal vacuolization forming a fatty rim on the inner side of the tubular basement membrane The vacuoles, which are generally separated by cytoplasmic septa, elevate, and partially surround the nuclei that are otherwise unchanged The fat is confined strictly to the epithelium of the proximal tubules, including the convoluted portions, the descending limbs, and the loops of Henle The lesion is diffuse, involving all of the nephrons Fat nephrosis, unlike the so-called lipoid nephrosis, is not accompanied by lipid deposits in the glomeruli, vessels, or interstitium

The fatty change that is associated with lobular or membranous glomerulonephritis (clinical "lipoid nephrosis") involves the same portions of the nephron, but the involvement tends to be irregular. In addition, the lipid is not basal in location but is distributed diffusely through the cell in a pattern of lattice-work The diffuse cytoplasmic lipid vacuolization is characteristic also of the fatty changes in the proximal tubules in amyloidosis, atrophic nephrosclerotic kidneys and particularly in the kidneys of diabetic glomerulosclerosis (plate 240). In the latter kidneys, in amyloidosis, and in those with lobular or membranous glomerulonephritis, the fat is, in part, anisotropic

## Mercurial Nephrosis

Mercuric chloride (mercury bichloride, corrosive sublimate, $HgCl_2$) is the compound responsible for most of the deaths from mercury The deaths are caused by accidental or suicidal ingestion or by the use of the bichloride as a vaginal douche or as an abortifacient. Cases of poisoning have been reported following the use of solutions of mercuric chloride in the irrigation of the field of a surgical operation, or as a cutaneous fungicidal agent. The minimal lethal dose for humans is difficult to estimate but 3 grains have caused death (Gonzales et al ) Whether or not renal damage was present in this latter case is not indicated. In other series (Peters et al.) patients recovered after taking at least 15 grains; none survived who had taken more than 4 tablets (30 grains or 2 Gm ). In dogs, 5 mg /Kg. intravenously invariably produced anuria and death (Sansum) and 20 mg./Kg by stomach was required for constant fatality (Haskell et al ) The human dose corresponding to the peroral lethal dose of dogs would be about 1.4 Gm. for a 70 Kg. adult, agreeing with the actual observations of most series.

Mercurial compounds other than mercuric chloride may be toxic The mercuric are more poisonous than the mercurous salts because of the greater solubility of the former. The mercuric salts include, in addition to the bichloride, mercuric iodide, mercuric oxide, mercurammonium chloride, mercuric salicylate, and mercuric cyanide. The mercurous salts are mercurous chloride (calomel), mercurous iodide and mercurous oxide. Practically all of these compounds have caused fatalities (Gonzales et al ). Apparently, in such instances, the mercurous salts are converted into mercuric form The organic mercurial compounds such as Salyrgan, Novarsal and Mercurochrome have also caused death on occasion The first two, Salyrgan and Novarsal, have resulted in sudden death during their administration intravenously as diuretics; no renal lesion attributed to their use has been found in these cases Mercurochrome has in the past been used intravenously as a bactericidal drug and has resulted in death with findings similar to those of poisoning by mercuric chloride (St. George)

### *Clinical Symptoms*

The clinical picture of mercury poisoning is characterized by stomatitis, abdominal pain and bloody, mucous vomitus if the poison has been ingested. Shortly afterwards, diarrhea and severe tenesmus appear owing to the development of a hemorrhagic colitis Death may occur in shock within the first 24 hours. If this period is survived, anuria or oliguria with mild to moderate albuminuria and scanty hematuria ensue. Glycosuria may also be present The urine is of low specific gravity even when oliguria is present; the urine contains hyaline, granular, and epithelial casts and granular epi-

# PLATE 112 Nephrosis of Proximal Nephron: Hyaline (Colloid) Granule Nephrosis

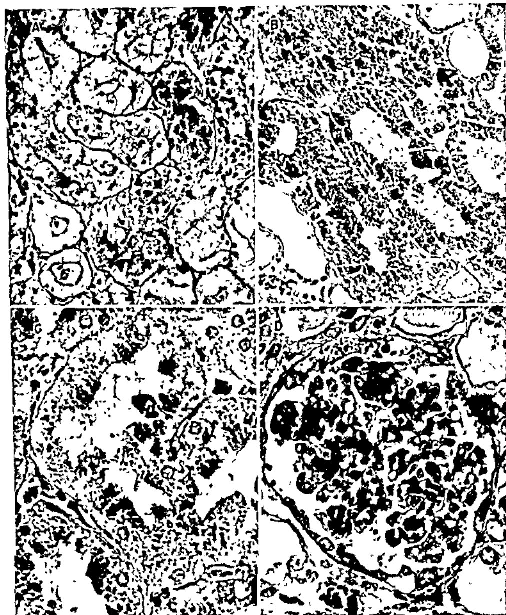


Fig A *Osmotic (sucrose) nephrosis* with hyaline granules in less severely altered cells

Fig C *Hyaline granules* resulting from intrinsic cytoplasmic alteration in a case of malignant nephrosclerosis

Fig B *Hyaline granules* in intrinsically altered epithelium of proximal convoluted tubule in a case of chronic glomerulonephritis

Fig D *Glomerular epithelial cells with hyaline granules identical with those in figures A, B, and C.* Obviously these granules in this location can not be attributed to reabsorbed protein

thelial debris If the diminution in urinary output persists, stupor, coma and uremia set in. In the anuric stage, hypertension may occur although it is often absent The level of blood chlorides may be markedly reduced. Death in this stage usually occurs from renal insufficiency associated with circulatory collapse although occasionally the colitis may be the major factor Treatment with BAL (British Anti-Lewisite; 2,3-dimercaptopropanol) is remarkably effective if instituted in the first few hours following poisoning BAL is presumed to act by successfully competing for combination with mercury against the sulfhydryl groups which are essential for the integrity of the cells. Death after renal insufficiency sets in is said to occur in about 12 per cent of cases

*Pathology*

*Gross appearance*

The kidneys are enlarged and soft In the early and later stages they may be markedly congested, in the intermediate phase, approximately the first week, they may be a pallid grey

*Histologic appearance*

The most conspicuous change in the kidneys affected by mercury bichloride is the degeneration, regeneration and calcification of the epithelial cells especially of the first portions of the proximal convoluted tubules The degenerated cells, some partially calcified, are cast off into the lumen as fragments or complete cells with granular or vacuolar degeneration Active epithelial regeneration takes place along with degeneration of adjacent or overlying cells The epithelial cells show mitotic figures, flattened basophilic cytoplasm with hyperchromatic nuclei, and small polypoid accumulations—all evidence of regenerative activity. The occurrence of calcification is not necessarily dependent on the degree of epithelial degeneration in the sense that instances of marked degeneration are noted without calcification despite an adequate lapse of time (plate 113)

It is assumed that when calcification does occur, it is localized to necrotic cells However, this is really not an observation but merely an unproved interpretation Calcification has been observed in mercurial nephrosis of dogs 24 hours after the mercuric chloride was administered (Hepler and Simonds). The precise chemical reasons for the calcification are not known. Necrosis of cells of the proximal tubules is not sufficient basis, nor are the level of blood calcium, pH, the time of action, or the dosage of the poison the determining factors. The role of phosphatase is not clear although it has been observed experimentally that regenerating tubular cells are resistant to the repeated action of mercuric chloride (as well as of uranium nitrate), and these cells are known to have a diminished content of alkaline phosphatase. Fat (Hepler and Simonds) or protein (Gomori) is thought to play a possible role in the calcification The calcium has a particular affinity for the nuclei of cells and we have seen calcification even of chromosomes of regenerating epithelial cells in mitosis. This latter observation indicates that regenerating cells in the kidney of the human are not completely resistant to the effects of the poison

Casts of protein, epithelial, cellular detritus, some inflammatory cells, and blood are found in the distal tubules. Calcified material in this debris is not commonly seen. Moderate dilatation of the lumens of the proximal tubules is frequently present. The interstitial tissue is often edematous and focally infiltrated in scattered areas with plasma cells and lymphocytes Occasionally a small focus of thrombophlebitis is found resulting from destruction of an adjacent tubule

As a rule, the glomeruli are histologically negative or show a slight focal increased endothelial cellularity Rarely, there is an associated acute diffuse proliferative glomerulonephritis In sharp quantitative contrast are the experimental findings of Hunter and Roberts who report frequent, "degenerative," functionally significant glomerular changes in rabbits and monkeys, poisoned with mercury bichloride, as well as with uranium nitrate. It is possible that actual photomicrographs might have been more convincing than the drawings which they appended In addition to the glomerular and tubular changes, we have found that the afferent arteriole, even in young normotensive individuals, may be acutely thickened by smudgy




FIG A *Mercury bichloride poisoning* (after 10 days) with extensive necrosis, calcification and desquamation of epithelium of proximal convoluted tubules Interstitial edema and inflammation are also present The tubules are only slightly dilated and the glomerulus is not remarkable

FIG B *Mercury bichloride poisoning* with similar clinical history (dosage and duration) as in case illustrated in figure A, showing extensive necrosis of tubular epithelium but without calcification

FIG C *Higher magnification* of section of figure A showing necrosis, polypoid regeneration and calcification of epithelium of proximal convoluted tubules

hyalin resembling somewhat the arteriolar change of malignant nephrosclerosis.

Finally, it is of interest to note that the preponderance of the degenerative change tends to be selectively localized to the peripheral portions of the cortex as opposed to the juxtamedullary regions This distribution suggests that the location of the damage may in part be determined by circulatory factors.

We have not seen an identical type and location of calcific deposits in association with the degenerative and regenerative histologic picture in human kidneys caused by chemicals other than mercurials However, similar calcification has been reported in human cases of bismuth poisoning (Weller), and in dogs poisoned with uranyl nitrate and potassium dichromate in 45 per cent and 25 per cent of animals respectively. However, as plates 113, 114, 115 and 116 show, extensive necrosis of tubular epithelium need not lead to calcification in these human cases of poisoning by potassium bichromate or potassium chlorate.

*Pathologic Physiology*

Experimentally, renal damage by mercuric chloride, as well as by uranium nitrate, may be prevented by ligation of the ureter This is not true of the changes produced by hypertonic solutions (Wilmer) The presumption is that the ureteral ligation soon stops glomerular filtrate so that the poison does not come in direct contact with tubular epithelium or, at least, is not concentrated there (Wilmer) The oliguria or anuria is usually explained on the basis of Richards' observations on frogs poisoned with mercuric chloride His direct measurements by pipets introduced into the nephron revealed a normal amount of glomerular filtrate which he assumed was more or less completely returned to the peritubular capillaries across the ineffectual necrotic epithelial barrier. It is not at all certain, however, that the conclusions from these experiments on frogs are applicable to conditions in man

As in the case of hemoglobinuric nephrosis, recovery is heralded by a rather sudden onset of diuresis, a reaction difficult to explain if the anuria is the result merely of marked tubular epithelial degeneration, regeneration of epithelium is not that spontaneous. The presence of shock early in the course and the sudden diuresis with recovery make it difficult to dismiss the thought that a vascular constrictive element is also at work, probably effecting a reduction in glomerular filtrate. No permanent renal damage follows clinical recovery from the poisoning although the ability to concentrate the urine may be impaired for weeks, just as in cases of hemoglobinuric nephrosis.

The mercury may be detected by chemical examination of the kidney as well as liver, feces, urine and the gastric contents if available early. Mercury may be found in the urine 3 to 24 hours after the poisoning (Lambert and Patterson) In addition to the renal damage, mercuric chloride produces diphtheritic, hemorrhagic necrosis of the mucous membranes contacted, as well as a hemorrhagic colitis that is pathologically like that of severe bacillary dysentery, the colitis of aplastic anemia or uremic colitis In the case of mercury poisoning, the colitis has been attributed to the excretion of the poison by the large bowel. This presumption has lead to the use of a cecostomy to drain the excreted mercury and to prevent further reabsorption.

Potassium Dichromate Nephrosis

The principal lesion of potassium dichromate ($K_2Cr_2O_7$) nephrosis is a marked necrosis of the tubular epithelium of the proximal portion of the nephron extending down to the loop of Henle. As with some other advanced necrotizing nephroses involving this portion of the nephron, such as those due to mercury bichloride and potassium chlorate, the damaged epithelial cells are more brightly eosinophilic than normal and the cytoplasm is converted into a mass of acidophilic hyaline granules As Opie has shown, the osmotic pressure of such cells is considerably reduced, and, on this basis, the hyaline granules may be formed The cellular detritus often fills the lumens of the proximal tubules, and, because of its coalescence, may resemble amorphous protein precipitate. Usually the desquamated masses in the lumens are surrounded by regenerating tubular epithelium Cast off cells in mitosis may be observed in the midst of the luminal debris The



FIGS A AND B *Potassium dichromate nephrosis* showing varying stages of degeneration, regeneration and desquamation of epithelium of proximal convoluted tubules The hyperchromatic cells are in the stage of regeneration

nuclei of the desquamated cells quickly become pyknotic, distorted, and finally disappear so that large casts of anuclear cytoplasm of sloughed cells, occasionally intermixed with leukocytes, occupy the lumens of the proximal tubules Focal, slight to moderate dilatation of these tubules is apparent. Some of the cellular debris reaches the collecting tubules, but not enough to cause significant obstructive change.

The interstitium is moderately edematous and there is a mild interstitial inflammation. The glomeruli are not remarkable. Some of the afferent arterioles, as in the mercury kidneys, show acute, acellular, diffuse, hyaline, acidophilic alteration (plate 114).

### Potassium Chlorate

Potassium chlorate ($KClO_3$) is used industrially in the manufacture of explosives and in medicine as a component of mouth washes Poisonings occur from accidental, suicidal or homicidal ingestion The symptoms are those produced by ingested corrosive poisons and include immediate vomiting, diarrhea, abdominal pain, dyspnea, cyanosis, convulsions, coma and death. Methemoglobin is formed and the urine may be colored dark by its excretion.

The renal histologic reaction (plate 115) is not that of hemoglobinuric nephrosis but of a proximal nephron nephrosis of a quality very much like that due to potassium dichromate, described previously, and to potassium bromate (neutralizer of "cold wave" lotion).

### Glycol Nephrosis

The toxic glycols and their formulas are listed in table 7. These compounds are used as detergents and preservatives and are employed in antifreeze agents, in the manufacture of lacquers, cosmetics, flavoring extracts and textiles. Diethylene glycol, the carbitols, dioxane and dipropylene glycol all have an ether linkage between *the molecules of glycol and they* all produce similar renal lesions in contrast to those caused by ethylene glycol, ethylene glycol diacetate and propylene glycol, which lack the ether linkage.

TABLE 7.—*The Toxic Glycols and Their Formulas*

| | |
|---|---|
| Ethylene glycol (antifreeze) | $HO\ CH_2CH_2\ OH$ |
| Ethylene glycol diacetate | $CH_3CO\ O\ CH_2\cdot CH_2\ O\ CO\ CH_3$ |
| Propylene glycol | $HO\ CH_2\ CH\ OH\ CH_3$ |
| Diethylene glycol (diglycol) | $HO\ CH_2\ CH_2\cdot O\cdot CH_2\ CH_2\cdot OH$ |
| Ethyl diethylene glycol (carbitol) | $C_2H_5\ O\ CH_2\cdot CH_2\cdot O\ CH_2\ CH_2\cdot OH$ |
| Methyl diethylene glycol (methyl carbitol) | $CH_3\ O\ CH_2\ CH_2\ O\ CH_2\ CH_2\ OH$ |
| Butyl diethylene glycol (butyl carbitol) | $C_4H_9\ O\ CH_2\ CH_2\ O\ CH_2\cdot CH_2\ OH$ |
| Diethylene dioxide (dioxane) | $CH_2\ CH_2$<br>O O<br>$CH_2\ CH_2$ |
| Dipropylene glycol | $CH_3\ OH\ CH\cdot CH_2\ O\ CH_2\ CH\cdot OH\cdot CH_3$ |

#### *Ethylene Glycol Nephrosis*

Ethylene glycol (antifreeze—$HO\ CH_2\ CH_2\cdot OH$) has been injudiciously drunk for its intoxicating effects, or consumed mistakenly, as in the cases in which it was inadvertently used in the preparation of coffee A number of fatalities have been reported The lethal dose is estimated at 100 cc., but survival has followed the consumption of 240 cc. Ethylene glycol is a colorless, odorless fluid, with a not unpleasant, bitter-sweet flavor It is about twice as toxic as propylene glycol and half as toxic as diethylene glycol.

*Clinical picture*

The early signs and symptoms of poisoning include severe vomiting, excitation simulating alcoholic intoxication, convulsions, severe pulmonary edema, prostration and shock If this initial stage, lasting up to about 24 hours is

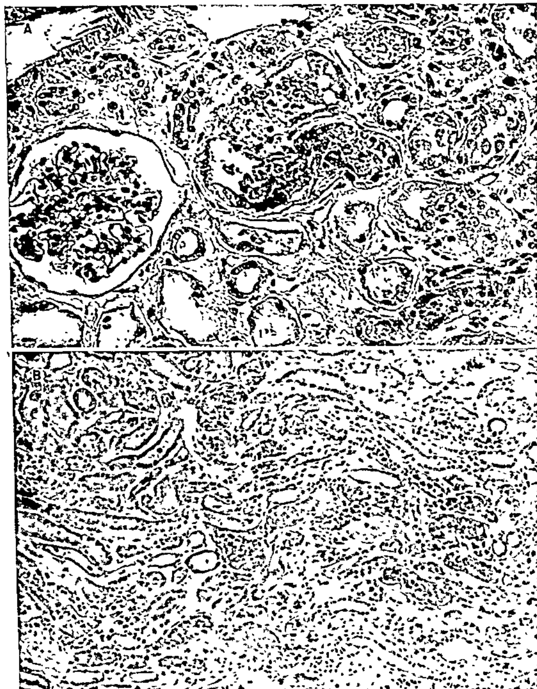



FIG A *Potassium chlorate nephrosis* showing necrosis of epithelium of proximal tubules The glomeruli are spared

FIG B *Potassium chlorate nephrosis* with extensive necrosis of tubular epithelium and obliteration of lumens of tubules by epithelial debris in association with focal interstitial edema and inflammation

survived, the patient develops signs and symptoms of renal insufficiency with death as the usual but not inevitable outcome. One case recovered completely despite the fact that the nonprotein nitrogen level of the blood reached 158 mg. per cent one week after the poisoning. Anuria may or may not be present in the initial stage but subsequently develops along with uremia

*Pathology*

The significant findings at autopsy are limited to the lungs, brain and kidneys. The lungs show marked congestion and bronchopneumonia. The brain is either grossly normal or edematous with flattened convolutions and occasional petechiae. Histologically, there is leptomeningeal perivascular infiltration with neutrophilic leukocytes, lymphocytes and histiocytes and minimal changes in ganglion cells Small refractile crystals may be demonstrable in the walls and lumens of the vessels, in the parenchyma and in the meninges. Often the crystals are not associated with inflammation in their vicinity

The kidneys are swollen but not otherwise remarkable The chief histologic features are (1) birefringent crystals of calcium oxalate in the lumens of proximal convoluted tubules and (2) diffuse dilatation of this portion of the nephrons The crystals are large, light yellow, and arranged as sheaves, prisms or rhomboids They frequently extend across the entire lumen of the dilated tubule which also contains granular protein precipitate (plates 117, 118). The epithelium of the proximal tubules may be somewhat flattened because of the dilatation but shows no significant degenerative or regenerative changes, despite apparent puncture by the needle-like crystals. The glomeruli are not remarkable except for dilatation of Bowman's spaces Mild focal interstitial mononuclear inflammation and edema are usually present.

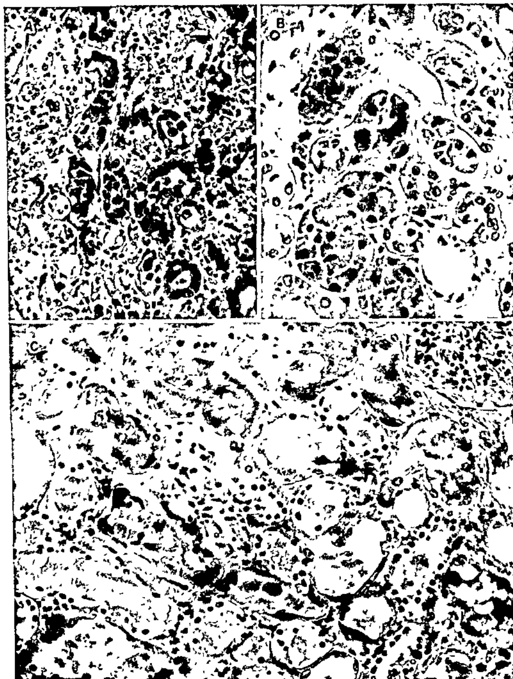
This is essentially the lesion produced experimentally by ethylene gylcol or by the diacetate. As would be expected, it is also the picture that follows the accidental ingestion of the corrosive poison, oxalic acid ($H_2C_2O_4 \cdot 2H_2O$), if the patient survives the initial stage of collapse. Propylene glycol, of the same group of compounds, produces, after intravenous injection, hemolysis, azotemia and a histologic picture of heme casts in the kidney resembling hemoglobinuric nephrosis (Kesten et al.).

Most observers have ascribed death in ethylene glycol poisoning to pulmonary edema and acute cardiac failure or to renal failure (Milles). Others (Pons and Custer) have attributed death primarily to lesions of the central nervous system and in only one of their 18 cases was "renal damage severe enough to contribute to a fatal outcome. . .in the other cases there was nothing beyond simple deposition of calcium oxalate " However, their conclusion is not supported by data on urinary output, specific gravity, or renal function tests, except for three determinations of urea nitrogen in two patients.

Evaluation of the role of the kidney in this poisoning can hardly be dismissed on such limited data The cerebral component may perhaps be a significant one in connection with shock and pulmonary edema, but the possibility of serious renal dysfunction ought not to be gainsaid in the presence of great numbers of partially obstructing crystals, with tubules showing varying degrees of internal hydronephrosis (plate 118 B), even if concomitant inflammatory or degenerative changes are absent It is true that much more data are needed for final evaluation, including information on potassium levels, and on other possible end-products of the glycols, inasmuch as only about 10 per cent of the ethylene glycol is accounted for by the calcium oxalate. As the situation stands, renal insufficiency appears to be the usual mode of death in those individuals who survive the first few days and expire several days later.

*Diethylene Glycol*

The general awareness of the toxicity of diethylene glycol was dramatically precipitated in 1937 by the occurrence of 76 deaths from the ingestion of 2 to 4½ ounces of an elixir of sulfanilamide. The elixir contained 72 per cent diethylene glycol The symptoms started 3 to 5 days after ingestion of the elixir and included nausea and vomiting, heartburn, abdominal cramps, diarrhea, facial edema, slight icterus,




FIGS A AND B *Atabrine nephrosis* The epithelium of the proximal nephron is in the various stages of degeneration The shrunken nuclei of some of these cells simulate those of plasma cells The atabrine had been used daily for months Atabrine nephrosis is a rare complication

FIG C *Necrosis with regeneration of cells* of proximal nephrosis in acute proliferative glomerulonephritis This marked tubular reaction may be confused with a primary chemical necrotizing nephrosis, when, in reality, the tubular changes are secondary to the glomerular ischemia The hyperchromatic cells are the regenerating ones (A F I P Acc 101695)

back pain, oliguria, anuria and uremia. Serous effusions were present in some of the patients. No hypertension or anemia was noted. Death occurred in 18 to 21 days There was considerable variation in response to the drug inasmuch as more than 100 persons took the toxic elixir without clinical effect.

*Pathology: liver*

The principal pathologic findings were in the liver and kidneys. The livers were not grossly altered except for moderate enlargement. The histologic picture of the liver is striking and is apparently specific for the group of glycols with the ether linkage The hepatic cells of about one third of the central portion of all lobules are uniquely altered. The alteration involves the collar of cells immediately about the central vein The involved zone is sharply demarcated from the outer two thirds of the normal peripheral parenchyma (plate 119 B). The granular acidophilic cytoplasm of the normal cell has been replaced in the involved zone by cells swollen by fluid in fine or coarse droplets that do not take the stain for fat or glycogen The nuclei are pyknotic. Remarkably enough, no noteworthy congestion or inflammatory reaction accompanies this parenchymal change in any part of the lobules.

*Pathology: kidneys*

The damage to the kidneys is even more striking In eight of twelve cases (Geiling and Cannon) bilateral cortical necrosis was present In all cases, however, there is a destructive coarse vacuolization of the cells of the proximal tubules The histologic stages in this degenerative process range from hyaline droplet swelling of the granules of the epithelial cells to complete disruption of the cell walls and extrusion of part or all of their contents (plates 119 A, 120 B) Cells are frequently seen in which the hyaline granules are in the process of being cast off from the cell into the tubular lumen. The vacuolization itself is of an order similar to that of the liver It is generally coarse resembling the glycogen vacuolization of diabetes mellitus, or of that associated with cholemic nephrosis or ulcerative colitis (plate 108 B), rather than the finely multiloculated vacuolar changes produced by fat or following the administration of hypertonic sucrose solution (plate 106). There is no mistaking the irreversibly destructive nature of the vacuolization wrought by diethylene glycol in contrast to the blander lipid, sucrose or glycogenic vacuolization. Diethylene and related glycols are markedly hygroscopic and this property may form the basis for what is tantamount to the destruction of the tubular cells by the suctioning of their contents into the tubular lumens.

The nuclei of the epithelium of the proximal convoluted tubules, again resembling those of the liver cells, are pyknotic, distorted and displaced to a corner of the cell, or altogether extruded into the lumen.

The glomeruli, except as they are involved in the cortical necrosis, show no significant change.

In the distal convoluted tubules, the only change of significance is the presence of isolated, deeply basophilic, spherical crystals with radiating lines The crystals are birefringent and are more or less the size of an epithelial cell of these tubules They are quite like those we have found associated with a great variety of acute viral and known chemical degenerations of the liver They resemble leucine but their precise nature is unproved

## Bismuth Inclusions

A rather unique variety of intranuclear and intracytoplasmic inclusion is found in the kidneys of patients who have received bismuth from such sources as bismocyanol (bismuth derivative of camphocarbonic acid) and bismuth tartrate Similar renal inclusions have been observed in rats injected intramuscularly with bismocyanol and sodium potassium tartrate (Pappenheimer and Maechling) The in- [illegible] and are

the nuclei and cytoplasm of the proximal convoluted tubules and are easily recognized with routine stains (plate 121). They are not necessarily associated with histologic evidence of cellular damage In a convincing set of photomicrographs, Pappenheimer and Maechling demonstrate the extrusion of these bodies from

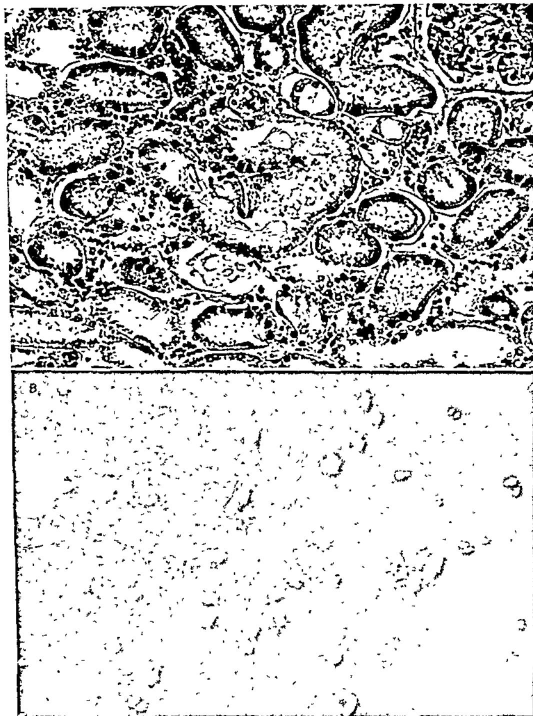



FIG A *Ethylene glycol (antifreeze) nephrosis* Crystals of calcium oxalate arranged in sheaves and protein precipitate are seen in lumens of proximal convoluted tubules

FIG B *Crystals of calcium oxalate* in proximal convoluted tubules are shown in photograph taken with incompletely rotated polarized light so as to indicate their position in the nephron If the initial cardiac failure, pulmonary edema and shock are survived, death is due usually to renal failure Encephalitis is said to account for some deaths

the nucleus to the cytoplasm of the tubular epithelial cell.

That these inclusions actually are bismuth compounds has not been proved. The inclusions are easily distinguished from proved (e g , encephalitic) epithelial viral inclusions (plate 121), and from the lesions of so-called "inclusion" disease (plate 122). The nuclear inclusions following lead poisoning (Blackman) are similar to those due to viruses

In addition to the specific inclusion bodies, calcification following necrosis of renal tubular epithelium has been reported after the injection of bismuth compounds in both humans and experimental animals (Weller). However, no calcification was noted by Pappenheimer and Maechling in the kidneys of either humans or animals treated with various bismuth preparations

### Inclusion Disease of Infants

In 1904, there were described, apparently for the first time, peculiar inclusion bodies in the tubular epithelium of infants (Jesionek and Kiolemenoglou, Ribbert). These inclusions were then regarded as protozoan, an impression that received more definitive confirmation from Smith and Weidman who identified the inclusions as a form of ameba which they termed *Entamoeba mortinatalium*. These inclusions were soon found in other organs, especially the parathyroid, pituitary and salivary glands; less often in the kidneys, bile ducts, liver, pancreas, lungs, rarely in the thyroid, epididymis, intestine and brain Their similarity to those cutaneous inclusions of varicella described by Tyzza in 1906 was first indicated by Goodpasture and Talbot in 1921 In the same year Lipschutz concluded that the intranuclear inclusions of herpes really represented specific reactions to a specific virus. This impression was extended to a generalization that nuclear Type A inclusions, similar to those under discussion, indicated a localization of the infective viral substances [Goodpasture (1929)] Because the virus has never been isolated or transmitted to animals, the proof of the viral nature remains inferential and incomplete

This hiatus in the evidence does not justify the skepticism accorded the viral concept of the lesions (Pinkerton). Morphologically similar inclusions in renal epithelium are said to be produced with lead and bismuth poisoning, and by certain aluminum and ferric compounds (Olitsky and Harford). However, the renal epithelial inclusions attributed to lead poisoning are stated to be acid-fast, in contrast to the viral inclusions (Wachstein) The latter are actually mildly acid-fast. Moreover, we find that the large, haloid, highly characteristic, inclusion bodies of "inclusion disease," within the epithelium of the distal convoluted tubules, are easily distinguished from the lead or bismuth lesions even in sections stained routinely with simple hematoxylin-eosin (plates 121, 122). Fat is present in the perinuclear, clear zone.

Inclusion disease of infants has not been diagnosed clinically. It occurs in the salivary glands of infants, mostly under one year of age, in about 12 per cent of routine autopsies of this age group, inclusions in the kidneys are found in about 1 per cent of autopsies of infants. Indistinguishable inclusion bodies are found in the salivary glands of guinea pigs (Pearson).

Involvement of the kidney gives rise to no signs or symptoms, but, as Pinkerton points out, the possibility exists that the cells with the inclusion bodies could be found by examination of the urinary sediment. This "inclusion disease" may be responsible for the death of infants, particularly on the basis of pulmonary and hepatic involvement (Vellios and Smith). [illegible]

Farlane: J. Path. & Bact 59: 385–398, 1947)

### Paroxysmal Nocturnal Hemoglobinuria (Marchiafava-Micheli Syndrome)

Credit is given to Marchiafava (1911) and to Micheli (1931) for clarifying as a separate entity the disease now known as the Marchiafava-Micheli syndrome, paroxysmal nocturnal hemoglobinuria, or chronic hemolytic anemia with nocturnal hemoglobinuria.

#### *Clinical Picture*

The disease occurs in previously well individuals mostly between the ages of 20 and 40 years, equally divided between the sexes, rather




FIG A *Ethylene glycol (antifreeze) nephrosis* with crystals of calcium oxalate in proximal convoluted tubules, the brush borders of which are clearly identifiable This patient consumed 200 cc of the poison (A F I P 116300)

FIG B *Ethylene glycol nephrosis* with dilatation of tubules (internal hydronephrosis) due to blockage by the crystals of calcium oxalate shown herein

than preponderant among males as formerly thought (Manchester) The youngest patient reported was 5 years old (Manchester)

The clinical picture is characterized by acute attacks of hemolysis and hemoglobinuria, coming on during sleep. It does not matter if the hours of sleep take place during the day or night Episodes of hemolysis may be provoked by infections, even mild upper respiratory tract infections, by the menses, by the administration of acid salts, or by abruptly curtailing alkali therapy. Exposure to sun, prolonged chilling, exercise, food, or a positive syphilitic serology (as in paroxysmal cold hemoglobinuria) have no bearing on the disease.

The clinical symptoms are those of anemia. Immediately after the attack, there may be headache, backache, and abdominal and muscular cramps Thrombosis of veins has been observed in about 25 per cent of cases (Ross).

Fatalities occur in most cases, in from 5 to 15 years, from thrombosis of large visceral veins, intercurrent infections, anemia, and operative mortality (Manchester) Hemoglobinuric nephrosis is not a part of the picture unless it follows an incompatible blood transfusion. Splenectomy and even transfusions are of little help as supportive measures and there is the added risk of the hemolytic reactions in the latter instance.

*Diagnosis*

The clinical diagnosis of paroxysmal nocturnal hemoglobinuria is confirmed by the demonstration of hemolysis of the patient's cells in the patient's or in normal serum acidified to pH 6.8 to 7.0. The hemolytic factor may be destroyed by heating the serum to 56° C. for 20 to 30 minutes There is no increased fragility to hypotonic saline, no spherocytosis, and the Donath-Landsteiner phenomenon does not occur. The defect is therefore in the patient's red blood cells rather than in the serum

There is no unequivocal proof that the pH or carbon dioxide combining power of the blood becomes lowered during sleep, although some data are available (Hastings and Eisele) The *in vivo* counterpart of the phenomenon of hemolysis with acidified serum in the test tube is ll unexplained Oxyhemoglobinuria, methemoglobinuria, and, in protracted cases, the diagnostically important feature of hemosiderinuria may be noted

*Pathology*

The kidneys, which are usually the site of deposition of hemosiderin after a period of years of this disease, are moderately enlarged and brown with hemosiderin (plate 123 A) Even grossly, it is seen that the hemosiderin is confined to the cortex including the columns of Bertin (plate 123).

Histologically, the hemosiderin is practically confined to the epithelium of the proximal convoluted tubules, unlike the distal localization of hemosiderin in hemochromatosis (plate 124) The pigment is fairly easily recognized in the routine sections by the refractile, hard-appearing, relatively irregular, sharply bordered granules The stains for iron (e g., Perl's stain) are strongly positive. However, with experience they can most often be distinguished in routine stains from granules of melanin, or from lipochromes that may be present in the tubular epithelium.

It has been generally assumed that the hemosiderin granules are engulfed in the process of athrocytosis by the proximal epithelial cells from the fluid in the tubular lumen The possibility that the hemosiderin is dissociated from the globin directly within the epithelium, and that the granules of hemosiderin are formed intracellularly, seems to have been discounted without good reason Actually, the hemoglobin released in the plasma in hemolytic episodes is in solution, and is not particulate It appears to pass the glomerular filter, and to present itself to the cells of the upper part of the proximal nephron in solution Lower in the nephron, with changes in pH and electrolytes, the hemoglobin may become particulate In principle, a similar type of reasoning applies to the presumed athrocytosis of "droplets" of protein from the lumens of the proximal tubules (page 216)

Heme casts, necrosis of tubular epithelium, or focal interstitial nephritis are not present, so that there is no histologic basis for confusion of this lesion with that of hemoglobinuric nephrosis Some hemosiderin may be present also in

# PLATE 119. NEPHROSIS OF PROXIMAL NEPHRON: DIETHYLENE GLYCOL (ELIXIR OF SULFANILAMIDE)

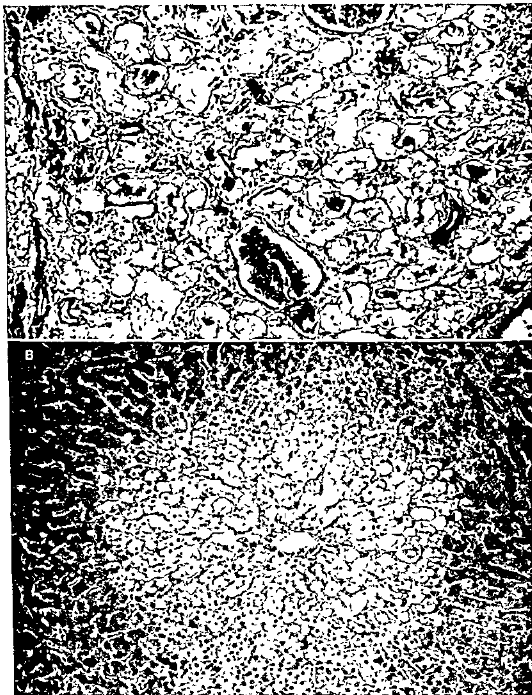



FIG A *Diethylene glycol nephrosis* The severely destructive hydropic degeneration of tubular epithelium, principally of the proximal nephron, is shown

FIG B *Hydropic degeneration of hepatic cells about central vein* is characteristic of toxicity due to diethylene glycol and other related glycols As indicated these vacuoles do not show evidence of glycogen or fat and this type of pericentral degeneration involves all hepatic lobules

the glomerular epithelium and in the interstitial macrophages. As mentioned, thrombosis of the *veins of the kidney (and other organs) may* occur.

### *Pathologic Physiology*

It is of considerable interest that the renal threshold for the excretion of hemoglobin (normally about 100 mg. per cent in plasma) may be progressively depressed to as low as 46 per cent of normal. In other words, normally, the plasma hemoglobin (molecular weight 68,000) that passes the glomerular filter is promptly reabsorbed across the epithelium of the proximal convoluted tubules When the tubular cells become loaded with hemosiderin, however, the reabsorption is hindered, as if the intracellular granules of hemosiderin were a mechanical barrier to the transfer of additional hemoglobin or its products Under this circumstance, therefore, hemoglobinuria occurs at low plasma levels of hemoglobin This barrier, remarkably enough, does not affect other substances, such as glucose, that are normally absorbed across this segment of the nephron If the interval between the hemolytic crises is prolonged, the opportunity is afforded for the tubular epithelial cells to rid themselves of the hemosiderin by its excretion in the urine as hemosiderinuria, or by its return to the blood At the same time, the renal threshold for hemoglobin correspondingly and gradually rises Actually this principle of saturation is the basis for studies of maximal clearance (i e , Tm's)

The presence of hemosiderin in the epithelium of the proximal convoluted tubules is not a qualitatively specific lesion Hemosiderin occurs in this location in other hemolytic anemias, and as a result of multiple transfusions It is remarkable, however, to note that in these latter conditions, there is, as a rule, a wide disparity between a small amount of *renal* hemosiderosis in contrast with the hemosiderosis of the liver, spleen and lymph nodes. Quite the reverse is true of the organs in paroxysmal *nocturnal hemoglobinuria*, so that this diagnosis may safely be suggested when conspicuous hemosiderosis is practically confined to the kidney (plate 124). For reasons that are altogether obscure, the renal hemosiderin in hemochromatosis, and in unusual instances of hemolytic anemias associated with marrow mast cells, selects the distal convoluted tubules (plate 124 C)

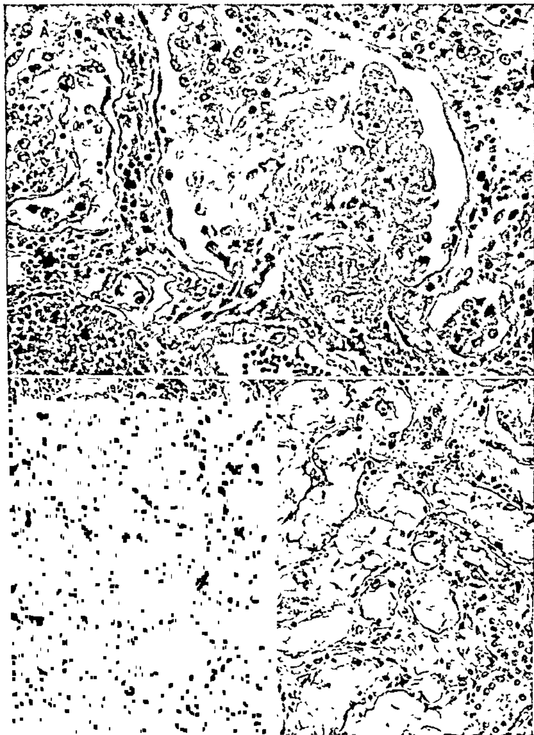
## Favism

Favism is another form of paroxysmal hemoglobinuria that has been rather loosely incorporated into the category of conditions that commonly cause hemoglobinuric nephrosis with death from renal insufficiency. This point of view deserves to be re-examined to see if it is justified by available documentation. Besides, "natural" experiments in patients with hemoglobinemia are of particular importance in throwing light on the pathogenesis of hemoglobinuric nephrosis. It is clear from the hemolysis that occurs in hemolytic diseases, such as congenital or acquired hemolytic icterus, and from paroxysmal nocturnal and cold hemoglobinurias, that hemolysis alone does not produce the dramatic picture of hemoglobinuric nephrosis with renal insufficiency In favism, at least two additional, perhaps critically pertinent, factors often operate in addition to the hemolysis: (1) allergy and (2) shock.

Favism has in most cases a familial background of the disease; it occurs in Sardinia, Sicily, and southern Italy. Rare cases have been reported in Palestine (Robinson), and even in the United States (McCrae and Ullery; Josephs). It results from inhalation of the blossom pollen dust or from the ingestion of the bean of the plant, *Vicia faba*, related to the lima bean family. This plant is cultivated extensively in some of the states, especially New

Fig A *Diethylene glycol nephrosis* showing thrombosis of glomerular capillaries and afferent arteriole as part of the associated bilateral cortical necrosis

Fig. B *Diethylene glycol nephrosis* is commonly combined with *bilateral cortical* necrosis as here indicated The necrosis is shown at the left and the characteristic tubular vacuolization is at the right The vacuolization simulates that seen in ulcerative colitis or dysentery (plate 108, figure B) but it is far more destructive




(Legends on facing page)

Jersey, New York, Illinois and California (Luisada) The reason so few cases of favism occur in this country is, therefore, not clear.

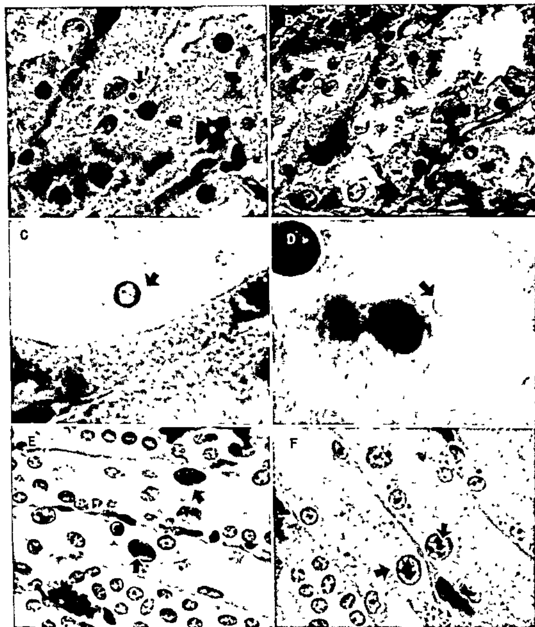
The disease is characterized by an acute onset of nausea, vomiting, fever, abdominal pain, pallor, icterus, vertigo, hemoglobinuria, and, in severe cases, rapid collapse and death in two to three days. The attack is said not to occur with the first contact with the bean nor in those who eat the bean regularly throughout the year. The onset of symptoms may take place within a few minutes after inhalation of the pollen, or may be delayed one to three days. In those countries in which favism is likely to occur, the diagnosis of blackwater fever enters the differential picture Death in about 8 per cent of cases (McCrae and Ullery) occurs from overwhelming hemolysis and shock, especially in children Rarely, death has been attributed to hemoglobinuric nephrosis but the evidence is incomplete. So very few necropsies of these patients have been recorded, and so sparse has been the documentation of the clinical cases from the renal point of view, that a definitive statement is not warranted on the data available. However it appears that the syndrome of hemoglinuric nephrosis, if it occurs at all in favism, is uncommon and is related not only to the overwhelming hemolysis which may destroy one of every five red blood cells, but to the associated shock and possibly also to the allergy. In this connection, it is pertinent to note the case of hemoglobinuria caused by the venom from multiple bee stings in which there was rapid recovery with no evidence of hemoglobinuric nephrosis (Kosalka).

### March Hemoglobinuria

A form of hemoglobinuria and hemoglobinemia, first described in 1881, occurs infrequently among previously healthy young men, after exercise such as walking, marching or running. It is a remarkable fact that in these same individuals exercise not taken in the upright position, such as cycling or swimming, does *not* precipitate an attack (Gilligan and Blumgart). With minor exceptions, for example backache, the only symptom of the disease is the observation by the patient of "blood" (hemoglobin) in his urine, anemia and icterus occur rarely. The hemoglobinuria is associated with hemoglobinemia which may reach levels as high as 220 to 230 mg per cent. No urinary suppression occurs in the uncomplicated disease, that is, hemoglobinuric nephrosis is clearly not a part of the picture. The course of the disease is benign and self-limited; the attacks cease spontaneously after a few months to a few years The episodes of hemoglobinuria may be induced at will with exercise, but there is no significant association with acidosis, syphilis, cold agglutinins, *detectable* fragility of red blood cells, sleep, malaria, infection, lordosis, or the ingestion of fava beans. There is no evidence of any form of desensitization as a result of repeated attacks. Striking results have been achieved therapeutically by the administration of ascorbic acid (Lubran and Sakula).

#### *Pathogenesis*

The cause of the hemolysis is unknown. The requirement of exercise in the upright position has led to the suggestion that the mechanism may be related to that concerned with orthostatic albuminuria. However, lordosis which is usually present in cases of orthostatic albuminuria is uncommon in persons with march hemoglobinuria, according to Lubran and Sakula Moreover, as these authors mention, march hemoglobinuria involves both kidneys whereas only the left kidney is said to excrete the protein in orthostatic albuminuria (Hinman) Finally, orthostatic albuminuria is not associated with march hemoglobinuria. It is known that a mild degree of hemoglobinemia of the order of 14 mg per cent occurs normally after severe exercise (Gilligan et al.) It appears established that the renal threshold for the excretion of hemoglobin is considerably lowered in instances of march hemoglobinuria from the normal of about 100 mg. per cent to about 30 mg. per cent. This fact alone does not explain the problem inasmuch as levels over 200 mg per cent are reached in this disease The predisposition of some individuals to develop an exaggerated hemolysis during exercise is explained by Lubran and Sakula on the basis of the discharge into the general circulation of a small percentage of fragile red blood cells by the excessively contracting spleen However, spon-




FIGS A, B, C AND D *Bismuth inclusions* (arrows) are in the epithelium or lumen of the proximal convoluted tubules They are not doubly refractile.

FIGS E AND F *Acidophilic viral inclusions* in the limbs of Henle from a case of St. Louis encephalitis (arrows).

taneous cures and the response to ascorbic acid are difficult to reconcile with this theory.

### Paroxysmal Cold Hemoglobinuria

Paroxysmal cold hemoglobinuria occurs almost exclusively in syphilitic individuals, principally congenital syphilitics, in only about 5 per cent of cases is there no clinical or serological evidence of syphilis The attack of hemoglobinemia and hemoglobinuria (oxyhemoglobinuria and methemoglobinuria) takes place in from a few minutes to seven or eight hours after the exposure to cold The exposure may be remarkably slight, cold drinks may start an attack. Rarely, as in cases of *virus pneumonia*, hemoglobinuria occurs as a result of the production of cold agglutinins in the absence of syphilis

The attack is very much like those of other forms of paroxysmal hemoglobinuria and consists of aching pains in the back and legs, abdominal cramps, usually chills and fever, and the passage of chocolate colored urine The specific diagnosis is established by the demonstration of an autohemolysin by the test known as the Donath-Landsteiner phenomenon. This test is performed with a 5 per cent suspension in saline of normal red blood cells, belonging to the same blood group as the patient's blood, to which are added equal parts of the patient's serum and fresh guinea-pig complement. The mixture is chilled for 10 to 30 minutes and is then warmed to 37°C for 30 minutes If the lysin is present, the blood is hemolyzed. The analagous *in vivo* reaction is known as the Rosenbach test in which hemolysis is induced by chilling the patient's hands or feet in ice cold water for 10 minutes

Hemoglobinuric nephrosis occurs with extreme rarity in association with this disease One case was recently reported by Sussman and Kayden but the complication was nonspecific Antiluetic therapy usually reduces the titer of the autohemolysin, and thereby eliminates the attacks.

In summary, paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome), paroxysmal cold hemoglobinuria, favism, and march hemoglobinuria represent diseases that are prognostically either quite benign or, when lethal, do not cause death by hemoglobinuric nephrosis except possibly in the rarest instances when the setting for such a complication is coincidentally just right. The proper setting may imply particularly shock, allergy, hepatic or prior renal damage.

### Hemoglobinuric Nephrosis

#### *Introduction*

Perhaps no disease of the kidney has given so many observers the impulse to record their impressions in the last decade as has the entity known as *hemoglobinuric* or *lower nephron nephrosis* (For reasons to be elaborated in this section, the original term "hemoglobinuric nephrosis" appears to us preferable to "lower nephron nephrosis ") The vast number of cases is accounted for not merely by World War II in which, for example, 10 per cent of autopsied [illegible]

military and civilian practice. These include the use of sulfonamides, and the availability and free use of blood for transfusions, with the increased opportunity for reactions resulting from a variety of incompatibilities. However, although the literature on the subject has, in these recent years, become voluminous, we seem not to have been brought appreciably closer to a solid understanding of these dramatically oliguric or anuric kidneys than we were a decade ago. And perhaps during this time, we have lost a little of our hold on the pathology of the kidneys in this condition.

#### *Etiology*

Hemoglobinuric (lower nephron) nephrosis may occur in a wide variety of conditions. These include incompatible blood transfusions, crush injuries, shock, reaction to sulfonamides, rapid hemolysis by the use of distilled water during operative procedures such as transurethral prostatectomy, uteroplacental hemorrhage, high altitude anoxia, heat stroke, blackwater fever (*P. falciparum*), mushroom poisoning, and burns; it may occur, too, in association with acute yellow atrophy, particularly that produced by known chemicals (for example, carbon tetrachloride, chloroform,




FIG A *Infantile inclusion disease* characterized by enlarged epithelial cells of distal convoluted tubules with acidophilic nuclear inclusions These are usually incidental findings at autopsy, but infrequently are responsible for death

FIGS B AND C *Epithelial inclusions* in lining of distal tubule with epithelial debris in lumen Inflammatory reaction is absent

FIG D *Epithelial inclusion in distal tubule* identified by intervening uninvolved epithelium This *distal* nephron nephrosis is placed in this section for convenience of comparison with other epithelial inclusions

avertin, and arsenic) Often included in the list of causes of hemoglobinuric nephrosis are alkalosis, and the effects of hemolytic agents, such as photodeveloper (hydroquinone and pyrogallic acid), and the paroxysmal hemoglobinurias (page 241). The clinical and histologic picture of the latter three conditions warrants their distinction not only from each other but also from hemoglobinuric nephrosis

The case of alkalosis cited as an illustration of lower nephron nephrosis was reported originally by McLetchie and deserves some reevaluation Alkalosis was present, to be sure, but the patient, who had been vomiting excessively, was also in extreme dehydration and circulatory collapse Death occurred during an operative procedure. Degenerative and calcific changes were found in the distal nephron but no heme casts were present Obviously, in the presence of severe dehydration, circulatory collapse, and probably chloride deficiency, mere alkalosis cannot be considered the basic cause of this clinical or histologic picture The clinical setting has been more or less as complicated in other case reports of "toxic nephritis" (Brown et al ) in which hemoglobinuric nephrosis has been attributed to alkalosis Moreover, Addis and his associates failed to produce renal damage in rats kept on high sodium bicarbonate intake for 300 days Renal damage is stated to be produced by chloride deficiency itself (Cuthbertson and Greenberg), but others (Kirsner and Knowlton) fail to confirm this conclusion. The latter also find that severe alkalosis does not produce functional or histologic renal damage They discount any significant functional effect of the alkalotic parenchymal nephrocalcinosis It is therefore suggested that alkalosis be omitted from the list of causes of hemoglobinuric nephrosis

The hemolysis and poisoning caused by photodeveloper result in shock, pulmonary edema and rapid death The renal histologic picture is easily distinguished from hemoglobinuric nephrosis (plate 131 A), by virtue of the thin, almost serous hemolyzed blood, rather than dense heme casts, present in the entire length of the nephron from Bowman's spaces to the collecting tubules The characteristic feature of paroxysmal nocturnal hemoglobinurias (Marchiafava-Micheli syndrome) is the abundant collection of hemosiderin in the epithelium of the *proximal* convoluted tubules (plate 124 A, B), rather than hemoglobinuric nephrosis. This same feature is qualitatively true, although to a lesser degree, of other forms of paroxysmal hemoglobinurias.

### *Clinical Manifestations*

The sequence of clinical signs and symptoms of hemoglobinuric (lower nephron) nephrosis naturally differs somewhat with the etiologic circumstances. Several of these will be considered

#### *Incompatible transfusions*

The reaction following the administration of *incompatible* transfusion depends on the titer of the isoantibody, on the amount of incompatible blood administered, on associated diseases, and on whether or not the patient is anesthetized Ordinarily, the patient responds immediately to the incompatible blood with chills, fever, backache, nausea and vomiting and occasionally urticaria The response to an incompatible transfusion may be completely obscured while the patient is under anesthesia Often the first indication of the incompatibility is the remarkably severe hemorrhagic tendency such patients develop, so that the enigmatic capillary oozing of blood from the surgical field may reach serious and even fatal proportions (Wiener and Peters) There quickly follow icterus, oliguria with hemoglobinuria, and retention of nonprotein nitrogen finally associated with uremia. In patients who develop the full-blown syndrome, death occurs in about 45 per cent of cases in 4 to 18 days. As with the crush syndrome, in those who survive, recovery is heralded with sudden diuresis in about 7 to 14 days. However, not all of the renal functions are immediately fully restored. The blood nonprotein nitrogen may take a month to correct itself completely, and the concentrating ability may remain impaired for several months

The minimal amount of incompatible blood that has caused a fatal hemoglobinuric nephrosis is in the neighborhood of 350 cc. (Bordley), although as little as 10 cc may cause symptoms (Eagle) The amount of incompatible blood




Fig A *Paroxysmal nocturnal hemoglobinuria* showing proximal tubules naturally outlined by deposits of hemosiderin in a slightly enlarged longitudinal section of kidney (Courtesy T H Ham, Charles Branch )

Fig B *Prussian blue reaction* on the section pictured above indicates by the darker areas the distribution of the hemosiderin in the cortical tissue

that can be administered without fatality depends on the titer of isoantibodies in the recipient This titer may be built up through isoimmunization by repeated transfusions so that subsequent transfusions may produce reactions not previously provoked by the same amount of blood. Moreover, certain diseases, such as leukemia, depress the titer so that as much as 1500 cc. of group B blood, for example, may be given to a recipient of group 0 without effect, according to Wiener and Schaefer. However, there are very few exceptions to the rule that the transfusion of 500 cc of incompatible blood causes death

*Crush syndrome*

In the *crush syndrome*, an individual may be partially buried by debris for several hours. Following his release he may get up, brush himself off and walk away with masked injuries, or, if a limb has been crushed, his traumatic shock responds to treatment. In either case, the symptoms of renal dysfunction begin to manifest themselves in a day or two. The urinary output diminishes, the urine is probably acid and colored by heme pigments (blood hemoglobin or myohemoglobin). The crushed limb swells, and may so dominate the picture as to prompt amputation Then lethargy, blurred vision, retinitis and hypertension occur along with mounting azotemia and uremia Complete renal recovery occurs with sudden diuresis in from 7 to 14 days in about 33 per cent of cases at this stage, according to Mallory, in the remainder, death with uremia terminates the picture in this period In air raids on London during World War II, it was estimated that the crush syndrome accounted for 5 per cent of the casualties There is a positive correlation between the depth of the shock and the extent of the injuries on the one hand, and the development of hemoglobinuric nephrosis on the other (Mallory)

*In addition to the crush syndrome, other* diseases of muscle lead to hemoglobinuric nephrosis. Acute paralytic myohemoglobinuria is a remarkable recurrent syndrome, characterized by an unusually painful swelling of skeletal muscles, either spontaneously, or after exercise, followed by fever, myohemoglobinuria, anuria and azotemia. Up to 1943, seven cases had been reported (Bywaters and Dible). Fatality from acute paralytic myohemoglobinuria occurs in a high percentage of the few human cases The corresponding disease in overexercised and overfed horses (paralytic equine myohemoglobinuria) leads to a mortality between 20 and 70 per cent At autopsy, the involved *necrotic muscles in the animals and in man*, have a color and texture resembling fish flesh, and the kidneys are indistinguishable from those of hemoglobinuric or myohemoglobinuric nephrosis. Bywaters and Dible noted the resemblance of the clinical course of acute paralytic myohemoglobinuria to that of fatal porphyruria. Apparently a disease similar to myohemoglobinuria is caused in man and cats from the ingestion of fish that have fed on certain cellulose industrial waste from a region in Germany The condition is known as Haff's disease, or bay sickness Uteroplacental hemorrhage may also lead to a fatal hemoglobinuric nephrosis

We have observed still another circumstance in which muscle injury in association with operative shock produced a hemoglobinuric or myohemoglobinuric nephrosis. A 35 year old man was maintained in a knee-chest position for six hours during an operation for removal of a herniated intervertebral disc. Death occurred in anuria and uremia seven days postoperatively The thigh muscles were acutely necrotic and the kidneys showed hemoglobinuric or myohemoglobinuric nephrosis. No spectroscopic studies on the urine or blood were done.

In other words, a wide range of circumstances and factors leading to necrosis of muscle, including spontaneous or preferably idiopathic myositis, uterine apoplexy, and massive crushing injuries *may all* be associated with renal changes that are histologically and, to date, physiologically indistinguishable. Precisely what the nature of the common chemical trigger is remains to be determined. The likelihood is that this trigger, which is activated in the syndrome following rapid destruction of muscle, is similar to that set off after incompatible transfusions, after extensive liver damage, during certain infections, and after the use of drugs and hemolytic agents.

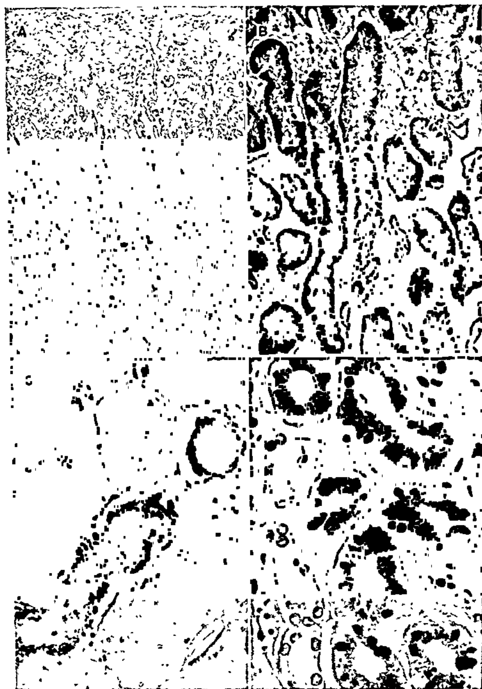



Fig A *Paroxysmal noctural hemoglobinuria* showing distribution of hemosiderin in the more darkly staining proximal tubules

Fig C *Hemochromatosis* with hemosiderin in the epithelium of the *distal* convoluted tubules in contrast to the site of hemosiderin deposits after intravascular hemolysis (Perl's stain for ferrocyanide reaction)

Fig B *Prussian blue reaction* demonstrating large amounts of hemosiderin within the epithelium of proximal tubules (Marchiafava-Micheli syndrome)

Fig D *Yellowish-brown lipochrome granules* may be confused with bilirubin and with the more refractile coarser granules of hemosiderin Their pathogenesis is not clear.

## *Pathology of Hemoglobinuric (Lower Nephron) Nephrosis*

### *Gross Appearance*

The kidneys are enlarged, often to between 250 and 350 Gm. each. Their consistency is flaccid rather than tense as from increased intrarenal pressure due to ureteral obstruction The capsules are easily stripped off their surfaces The sectioned surfaces are moist and smooth and tend to bulge over the cut edge of the capsule This tendency of the parenchyma to protrude beyond the capsule has been interpreted as indicative of an increased intrarenal pressure that might be relieved by decapsulation Evidence in support of this interpretation has recently been advanced by manometric data on intrarenal pressure (Peters) It appears more likely, however, that the occasional beneficial result from decapsulation is more dependent on interference with the renal nerve supply than on the relief of parenchymal tension

The cortices are widened and pale in contrast to the medullary pyramids which are streaked bright red, not by hemoglobin in the tubules, as some believe, but by the congested vasa recta and peritubular capillaries (plate 127).

### *Histologic appearance*

It would appear that the abundant material pretty universally available would eliminate any major disagreement as to the facts of the histologic appearance of hemoglobinuric nephrosis. Nevertheless, basic divergence in the simple reportorial descriptions exists. It is acknowledged that the histologic pattern is identical in hemoglobinuric nephrosis following incompatible transfusions, shock, crush or whatever cause This pattern consists of:

1 *Casts of hemoglobin (or a closely related pigmented globin) in the distal convoluted or collecting tubules* In practically all instances sections of medulla reveal casts in the collecting tubules in the vicinity of the pyramidal apex. These casts are usually fairly numerous but are often not sufficient to account for renal insufficiency on the basis of obstruction of nephrons. The presence of a few casts of hemoglobin in the lumens of distal convoluted tubules situated close to glomeruli does not of itself justify the diagnosis of hemoglobinuric nephrosis. This latter condition is found fairly commonly in infectious diseases particularly (Allen and Spitz) and is not responsible for significant renal dysfunction

The distinction of the brown granular hemoglobinuric cast from casts of myoglobin (presumed to occur with the crush syndrome) can not be made with routine stains Spectroscopic studies have been applied to blood and urine but the results have not been altogether satisfactory, in part because of the rapidity with which myoglobin disappears from the blood The renal threshold for myoglobin is 15–20 mg per 100 cc. of plasma in contrast to slightly over 100 mg. per cent for blood hemoglobin The rate of clearance of myoglobin is about 25 times more rapid than that of blood hemoglobin (Yuile et al ). As stated, the pigment casts of blood hemoglobin and muscle hemoglobin are histologically indistinguishable. Moreover, myohemoglobin, as Millikan points out, is a true hemoglobin, and actually constitutes one fourth of the total hemoglobin of the body. However, there are certain other differences between blood and muscle hemoglobin These are as follows (Millikan):

(*a*) The myohemoglobin does not normally circulate but is found in the muscle fibers, unless released by their rupture

[illegible]

(*c*) The spectroscopic absorption bands of myo- [illegible]

to oxygen

(*e*) Myohemoglobin has only one iron atom per molecule instead of four

(*f*) Myohemoglobin is much more resistant to alkali denaturation than blood hemoglobin

(*g*) The precipitin reactions are specific for each

Although these differences are unquestionably definite, they do not render inappropriate the application of the term "hemoglobinuric

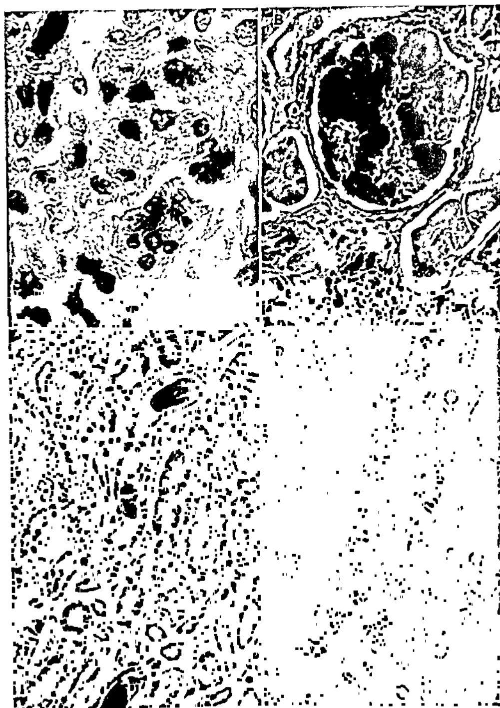



FIG A *Malarial pigmentation* in glomerular endothelial cells

FIG C *Melanin casts* in distal convoluted tubules in a case of melanocarcinoma

FIG B *Melanin pigmentation of melanocarcinomatous cells* metastatic to glomerulus

FIG D *Melanin granules* in epithelium of proximal convoluted tubules in a case of melanocarcinoma (unstained section).

# Nephrosis of Proximal and Distal Nephron: Hemoglobinuric (Lower Nephron) Nephrosis, Crush Syndrome




Fig. A. *Acute myositis* with necrosis and calcification following a crush injury associated with hemoglobinuric nephrosis

Fig B *Kidney of crush syndrome* with hemoglobin-like casts, focal interstitial edema and inflammation, and dilatation of Bowman's spaces with proteid precipitate

Fig C *Pigment casts* (possibly myoglobin) in distal nephron in a case of crush syndrome Tubular epithelial degenerative changes are present about casts

Fig D. *Crystals of hemoglobin* in experimental hemoglobinuric nephrosis (Courtesy, Dr Robert S Haukhol )

nephrosis" as applied to the crush and related syndromes (e g, incompatible transfusions, blackwater fever)

A considerable problem at times is the differentiation of casts of hemoglobin from those of bile in cholemic nephrosis or even, occasionally, from ordinary granular proteid casts In routine sections stained with hematoxylin and eosin, casts of bile are not always as unmistakenly green as is often thought, nor are the heme casts always characteristically brown The Lepèhne and cyanol stains which make use of hydrogen peroxide and benzidine in the staining of hemoglobin in paraffin sections are not nearly as satisfactory in practice as the literature indicates

2. *Tubular epithelial change* Because of the belief that the tubular epithelial degeneration in the distal portion of the nephron is the most significant change, the term "lower nephron nephrosis" has been applied to this renal disorder, previously called "hemoglobinuric nephrosis" (Lucké) Degenerative and regenerative changes certainly may be noted in distal convoluted and collecting tubules (plate 128 B) In some instances, however, this change is conspicuous, and in others, with a *similar clinical picture in terms of degree and duration, no such tubular damage is observed* In the majority of cases, the degeneration of tubular epithelium is not quantitatively, or even qualitatively, pronounced Nor is this evaluation of the extent of the tubular damage refuted by the photomicrographs used even by those who place great emphasis, not only on its occurrence, but on the role of such damage in the production of anuria or oliguria Histologically intact tubular epithelium about the heme casts of hemoglobinuric nephrosis is so common a finding (plate 128, 129 A) that it appears unlikely that whatever tubular epithelial damage does occur is produced by these casts As a matter of fact, otherwise similar renal lesions and clinical pictures may occur in the absence of heme casts (Ayer and Gauld, McLetchie, Young) Indeed, some of the most obvious tubular degeneration when it is present, occurs not about the pigment casts but in the region of the proteid casts in the distal convoluted tubules

3 *Interstitial reaction* Focal interstitial nephritis with inflammatory cells and edema is an almost constant feature of fatal hemoglobinuric nephrosis The interstitial edema is principally cortical, the inflammatory cells occur in foci chiefly at the cortico-medullary junction and in the medulla, although the upper cortex may also be involved The inflammatory cells are usually lymphocytes, plasma cells and histiocytes, in some instances eosinophilic leukocytes predominate and these do not necessarily represent a reaction to a drug The suggestion that an allergic element existed in hemoglobinuric nephrosis was made by Kimmelstiel

4 *Proteid casts* Weakly acidophilic, irregularly outlined casts of homogeneous density are often present in the distal convoluted tubules usually of the cortex As a rule, however, they do not appear to be sufficiently numerous to interfere significantly with renal function, nor is there an obstructive dilatation of the proximal portions of the nephrons in which they are located In the cases resulting from reactions to sulfonamides, crystals of these drugs may be embedded in the casts Other crystals closely simulating the structure of acetylated sulfonamides may be found in the kidneys of patients with hemoglobinuric nephrosis who did not receive sulfonamide therapy. These crystals are birefringent, greenish-yellow to blue black, the latter are calcified Their precise nature is not known, although as we have noted, they resemble the crystals of leucine, and are often found in association with acute, destructive diseases of the liver (plate 134 B)

The distal convoluted tubules with or without their casts may be ruptured, surrounded by inflammatory cells or foreign body granulomas (plate 143C) The veins at this level (usually arcuate veins), are closely applied to the distal tubules which may herniate into the venous lumens and frequently cause thrombophlebitis (plate 143 A)

*Miscellaneous* Other inconstant features include glomerular ischemia and proliferative glomerulitis, dilatation of the proximal convoluted tubules with loose granular protein precipitate in their lumens, fatty change in the epithelium of the proximal tubules and increase in the size and number of the granular cells of the juxtaglomerular apparatus (according to Goor-

## PLATE 127. Nephrosis of Proximal and Distal Nephron: Blackwater Fever (P. *Falciparum*)



*Magnified (14X) gross section of cortico-medullary region of kidney in blackwater fever* The dark streaks of the medulla are really radial peritubular blood vessels rather than tubules filled with casts of hemoglobin (A F I P Acc 37800 ) *Histologic* sections in figures A and B, plate 128

PLATE 128. NEPHROSIS OF PROXIMAL AND DISTAL NEPHRON: HEMOGLOBINURIC ("LOWER NEPHRON") NEPHROSIS




FIG A *Blackwater fever* with casts of hemoglobin and associated focal acute interstitial nephritis

FIG B *Polypoid tubular regeneration* of epithelium of collecting tubules in blackwater fever

FIG C *Hemoglobinuric ("lower nephron") nephrosis* caused by sulfathiazole therapy

FIG D *Hemoglobin casts* with associated purulent exudate in collecting tubules in blackwater fever

FIG E *Hemoglobinuric nephrosis* associated with acute yellow atrophy of the liver secondary to poisoning by carbon tetrachloride In none of the latter three instances (figures C, D, E) is there significant epithelial necrosis

maghtigh). The occasional dilatation of the proximal tubules (plate 142 B) is attributed to the obstructing heme casts rather than to the coagulum of protein found in the distal convoluted tubules.

### *Pathologic Physiology of Hemoglobinuric (Lower Nephron) Nephrosis*

One of the key physiologic problems in need of clarification is the mechanism of oliguria and anuria in hemoglobinuric nephrosis. The point of view generally held (Lucké; Dunn et al., Bywaters and Dible) is that adequate glomerular filtration occurs, but that in its passage down the nephron, the filtrate is reabsorbed across the necrotic tubular epithelium into the peritubular capillaries. This entirely inferential explanation has won general favor because of three attendant circumstances: (1) the direct and brilliant observation by Richards that glomerular filtration is unimpaired in the kidneys of frogs poisoned with mercury bichloride, (2) the widely and uncritically accepted assumption that extensive tubular epithelial necrosis is constant in "lower nephron" or hemoglobinuric nephrosis and (3) the relative paucity of glomerular histologic changes.

In criticism of the use of this evidence, it is suggested, with regard to Richards' observations (assuming the findings in frogs are transferable to man) that mercury bichloride produces an admittedly constantly severe degree of tubular necrosis in contrast to that of hemoglobinuric nephrosis. Moreover, the tubular necrosis resulting from bichloride poisoning affects the *proximal* and not the "lower nephron," a differentiating fact not prominently cited when Richards' experiment is used as supporting evidence for the hypothesis of "tubular oliguria." Finally, there is actually no positive evidence, even if the tubular basement membrane were stripped of its epithelium, that oliguria or anuria would result from reabsorption of filtrate. One must question the validity of the hypothetical mechanism of passive diffusion which accounts for the complete transfer of the glomerular filtrate across even a naked tubular basement membrane of the *distal* portion of the nephron. This skepticism is further justified by the presence of oliguria and anuria in hemoglobinuric nephrosis *without* pronounced epithelial necrosis. Furthermore, to explain the sudden diuresis which heralds recovery in these patients, it seems necessary to presuppose a correspondingly sudden healing of the tubular epithelium. This manifestly does not hold and could not occur. Nor does the assumption that tubular epithelium in hemoglobinuric nephrosis fails to regenerate until the tenth day appear warranted in view of observations on the more rapid regenerating capacity of epithelium in this and other diseases. It is true that the specific gravity of whatever urine is formed is at a fairly constant level, in the vicinity of 1 010. This fact indicates an incapacity of the tubules to concentrate the glomerular filtrate. A disturbance in tubular concentrating capacity is not necessarily indicative of a total or nearly total transference of fluid from the tubular lumen to the peritubular capillaries. After all, the proximal tubules are chiefly responsible for the concentration of glomerular filtrate, and the epithelium of this portion of the nephron is generally admitted to be structurally intact, as indicated by the term "lower nephron" nephrosis. The fact is that interference with tubular concentrating ability need not imply necrosis of tubular epithelium. Indeed, this function is often not completely restored in cases of hemoglobinuric nephrosis until weeks after organic residua of the disease are gone.

### *Mechanism of anuria*

What, then, is the pathogenesis of the oliguria or anuria in hemoglobinuric nephrosis? *A diminution or cessation of glomerular filtration* seems to be the more plausible answer. However, the proof for this mechanism is as difficult to establish at this time as the tubular reabsorptive concept is vulnerable to refutation. Clearance (Goormaghtigh) and histologic studies (French) suggesting glomerular ischemia do not constitute positive proof. The fact with regard to the histologic demonstration of glomerular ischemia is that, although it may occasionally be observed, many cases simply do not show this glomerular change. Moreover, an equivalent amount of glomerular alteration may be found in cases of acute focal or

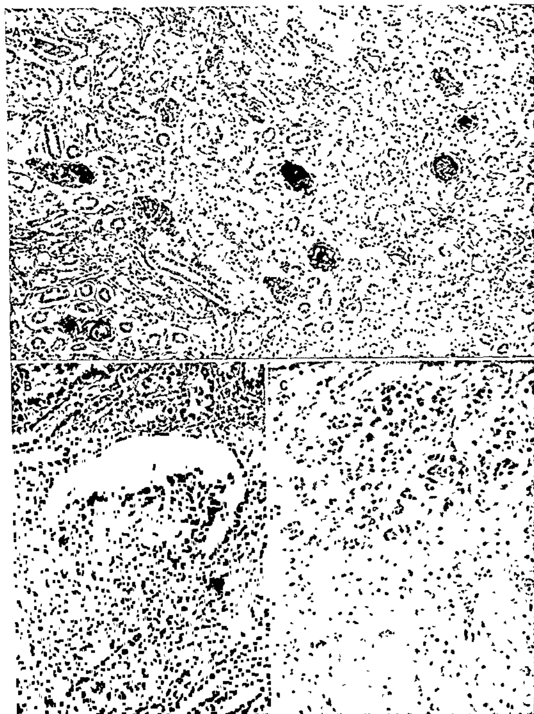



FIG A *Hemoglobinuric nephrosis* due to reaction to sulfathiazole

FIG B *Thrombophlebitis of arcuate vein* is found in hemoglobinuric nephrosis of a variety of causes

FIG C *Necrosis of anterior lobe of pituitary gland* in postpartum transfusion reaction with hemoglobinuric nephrosis



FIG A *Acute hemorrhagic glomerulonephritis* with red blood cells, some laked, in Bowman's space and in distal nephron The proximal tubules do not contain blood

FIG B *Acute exacerbation of chronic glomerulonephritis* with red blood cells and hyaline casts in collecting tubules

FIG C *Erythroblastosis fetalis* with casts of partially laked red blood cells in collecting tubules

FIG D *Erythroblastosis fetalis* (higher magnification of figure C) Partially fragmented as well as nucleated red blood cells in collecting tubules

FIG. E *Cholemic nephrosis* with bile casts in distal convoluted tubules Bile casts may be indistinguishable from hemoglobin or myoglobin casts in routine sections and often with special stains

FIG F. *Red blood cell casts* in collecting tubules from a case of thrombocytopenic purpura

acute diffuse proliferative glomerulonephritis without anuria or striking oliguria However, the experimental observation of glomerular ischemia with stimulation of splanchnic nerves (Bieter), glomerular hyperemia with sectioning of these nerves (Bieter), and the diversion of blood in shock from the kidney to other "more vital" areas, suggest that oliguria and anuria occur in hemoglobinuric nephrosis because so little filtrate passes through the glomeruli The shock that is the great common denominator of these cases diverts much of the huge proportion of blood that normally circulates through the glomeruli (25 per cent of the cardiac output) into other organs, as stated previously. There is beginning to accumulate considerable doubt that, in man at least, this divergence is effected by shunting the blood away from the cortical glomeruli to the juxtamedullary glomeruli The finding of congested outer cortical glomeruli lends support to the doubt In other words, there appears to be an over-all reduction in renal blood flow in hemoglobinuric nephrosis

Although those observers who postulate the tubular origin of oliguria and anuria in hemoglobinuric nephrosis stress the common and important role of shock, they do not at the same time, incorporate in their concept some of the striking physiologic effects produced on the glomeruli by shock For example, Lauson, Bradley and Cournand find that the glomerular filtration and effective renal plasma flow are significantly and consistently reduced in proportion to the degree of shock, and that the degree of oliguria reflects the rate of glomerular filtration which, in turn, is related to a reduction in renal blood flow The rapid—if only occasional—response to sympathetic block by the local or intravenous use of procaine would seem to be additional evidence of a vasoconstricting mechanism as a cause of the anuria, rather than tubular backflow (Fries, Langeron et al)

*Auxiliary pathogenetic factors*

It is entirely likely that auxiliary factors contribute to the renal embarrassment The heme or related pigment casts probably do not usually play a significant role in the dysfunction, but, on occasion, they are so abundant and so compact in the strategically located collecting tubules that they may infrequently produce the physiologic equivalent of a partial internal hydronephrosis (plate 142 B). That this is not common is attested to by the absence of a mass of hemoglobin casts pried loose into the urine at the time of diuresis and recovery.

The interstitial edema and interstitial infiltration may in some instances be of appreciable degree, and may further compromise renal function The thrombophlebitis and tubular coagula rarely seem to be sufficiently abundant to interfere significantly with function

Because of the conspicuousness of hemoglobinuria and of the heme casts in the histologic sections of many of these kidneys, much experimental effort has been devoted to a determination of toxicity of hemoglobin and myoglobin and related compounds. Pure hemoglobin as well as pure myoglobin circulating in the blood stream is not toxic for humans (Anderson et al, Bing) Nor is this fact altered by rendering the urine acid as is demonstrated by patients in hemolytic crises from paroxysmal nocturnal hemoglobinuria, who have been given ammonium chloride without the development of hemoglobinuric nephrosis This phenomenon is of interest because it has been assumed that the acidity of the contents of the lower nephron is responsible for the precipitation of the heme casts, an assumption that has led to widespread, often excessive, therapeutic use of alkali in cases of hemoglobinuric nephrosis Actually, fatalities from incompatible transfusions or blackwater fever may occur with persistently alkaline urine Nevertheless, it is still considered good practice to keep the urine alkaline Some observers have suggested that the tubular injury is a requirement for the precipitation of the heme casts (Yuile, Steinman, Hahn and Clark) However, heme casts are noted in the kidneys with hemoglobinuric nephrosis in the absence of associated histologically evident tubular damage.

When the many disparities are taken into account, there remains the common impression that it is not the hemoglobin or myoglobin, *per se*, that causes the renal dysfunction. Other potentiating, or synergistic factors may exist

in the form of urinary pH, oliguria, shock, vasoconstricting agents, adenosine phosphates, porphyrins, or porphyrin-like substances, and nephrotoxic chemicals produced as a result of hepatic dysfunction Even the ferrihemate (or ferrihemate and albumin, i e, methemalbumin) is considered by Anderson to exert its effects on the kidney in blackwater fever, not by its direct damage to the nephron but by its vasoconstrictive and thrombogenic effects The nephrotoxic effects of hepatic origin are suggested by the high incidence of hemoglobinuric nephrosis in association with acute yellow atrophy, particularly following carbon tetrachloride poisoning However, of all the factors potentiating the hemoglobinemia or myohemoglobinemia, the shock, with its attendant renal vasoconstriction and extrarenal diversion of blood flow, seems of first line importance

*Terminology*

It is not especially important whichever, name is given to the renal disease under discussion, so long as the disease is understood. The term "lower nephron nephrosis" (versus hemoglobinuric nephrosis) has in recent years achieved considerable popularity Nevertheless its following limitations ought to be set down.

1 There are many "nephroses" of the lower nephron, including those due to myeloma, gout, sulfonamides, nephrocalcinosis (secondary to alkalosis, bony lesions and hyperparathyroidism), uric acid, and hepatic diseases (cholemic nephrosis) Each of these conditions is a lower nephron nephrosis in a sense as complete as, or more definitive than, hemoglobinuric nephrosis

2 The proximal portion of the nephron is also occasionally involved with focal necrosis in hemoglobinuric or "lower nephron nephrosis" McManus states that there is a reduction in alkaline phosphatase in the proximal nephron in hemoglobinuric nephrosis and so suggests that "lower nephron nephrosis" is a misnomer

3. The necrosis of the tubular epithelium of the distal nephron is often inconspicuous

4. The renal dysfunction cannot be convincingly explained on the basis of the necrosis of the distal tubular epithelium, or of the casts in the lower part of the nephron. Hence, the designation "lower nephron nephrosis" focuses undue attention on the distal nephron from the point of view of functional and therapeutic investigations

5 Casts of hemoglobin or the closely associated myohemoglobin are, after all, the conspicuous and constant feature of hemoglobinuric nephrosis, or so-called "lower nephron nephrosis" The very few cases of so-called "lower nephron nephrosis" in which such pigment casts are absent, as in alkalosis, need to be re-evaluated in the manner indicated in this section.

For these reasons chiefly, the term "lower nephron nephrosis" seems not to have advantages sufficient to displace the pre-existing name, "hemoglobinuric nephrosis."

## Cholemic Nephrosis

### *Introduction*

The term "cholemic nephrosis" has come to have various and confusing connotations. Unlike some other unhappily chosen names of renal diseases, the difficulty with "cholemic nephrosis" is not that it fails to signify the particular renal structure at fault, but that the functional significance of this broad and ill-defined histologic entity has not been thoroughly clarified Another limitation of the use of the term "cholemic" is that occasional cases may occur in the absence of jaundice, although in the presence of hepatic damage

To the clinician as well as to the pathologist, one form of cholemic nephrosis is the more nebulous renal component of the *hepatorenal syndrome* The hepatorenal syndrome refers to several clinical variations of the postoperative course of patients who have had an opera-

FIG A *Hemolyzed blood* in Bowman's space and in distal tubules following accidental ingestion of one tablespoonful of hydroquinone with pyrogallic acid Death in 48 hours

FIG B. *Hemorrhage* into calyces and pelves in aplastic anemia Incidentally the bulk of the pelvic hematoma may simulate neoplasm by pyelography.

PLATE 131 DIFFERENTIAL HISTOLOGIC DIAGNOSIS OF HEMOGLOBINURIC NEPHROSIS. PYROGALLIC-ACID—HYDROQUINONE POISONING



(Legends on facing page.)

## PLATE 132. NEPHROSIS OF PROXIMAL AND DISTAL NEPHRONS: CHOLEMIC NEPHROSIS (CARBON TETRACHLORIDE)





FIG A *Acute yellow atrophy due to carbon tetrachloride poisoning* The necrosis is central and is associated with moderate fatty change

FIG B *Kidney from a case* of carbon tetrachloride poisoning with cholemic nephrosis

FIG C *Kidney from a case of cholemic nephrosis* due to carbon tetrachloride with bile casts in the distal nephron and mild osmotic nephrosis in the proximal tubules.

tion done on some part of the biliary system Stated summarily, these patients expire early (in the first 2 or 3 days) with icterus, coma and hyperpyrexia, or late (7 to 14 days) in their postoperative period with fever, interference with biliary drainage and with what is regarded as hepatic and renal insufficiency, including oliguria and azotemia In the early deaths, no organic renal changes are reported either in man or dog (after ligation of the hepatic artery) (Sutton), in deaths occurring later, cholemic nephrosis is found. There is no doubt that a great number of diagnoses of hepatorenal syndrome would not be made if a postmortem examination were done The reason is that many cases that are called "hepatorenal" syndrome clinically, are found at autopsy to have clearcut organic reasons for death which were not previously suspected These causes include hemoperitoneum, bile peritonitis, ligation of the hepatic artery with hepatic infarction, or some other unforeseen complication. But even when these are subtracted there remains a significant number of instances that must be retained even by the pathologist in the category of hepatorenal syndrome In these cases, there is invariably jaundice, usually severe, with the clinical picture closely akin to hemoglobinuric (lower nephron) nephrosis

*Pathology*

With this orientation, is it then possible to define cholemic nephrosis pathologically? In any event, the individual pathologic changes are these

Grossly, the kidneys are swollen and diffusely bile stained The diffuse green coloration may not be completely appreciated until after the tissue has been fixed in formalin Except for the icteric tinge, the sectioned surface resembles that of the kidney with hemoglobinuric nephrosis, it is moist, the cortex is widened and sharply delimited from the medulla and the medulla is radially streaked with congested vessels (plate 132 B).

Histologically, the changes are primarily tubular These changes consist of

1 granular bile staining of the epithelium of the proximal portion of the nephron down to the loops of Henle (plate 134 D),
2 gross hydropic vacuolization of the cytoplasm cells of the proximal convoluted tubules with without conspicuous nuclear change (plate A, 134 B) similar to that seen in cases of ulce tive colitis (plate 108 B),
3. infrequently, frank necrosis of epithelium w evidence of regeneration (plate 133) within proximal convoluted tubules;
4 bile casts, occasionally indistinguishable fr hemoglobin casts, in the distal convoluted a collecting tubules (plate 134 A),
5 focal interstitial infiltration of lymphocytes, tiocytes and a few plasma cells,
6 yellowish brown spherical amorphous and cr talline bodies usually in the distal convolu tubules (plate 134) but occasionally definitely the proximal tubules (plate 138 F)

The amorphous bodies are homogeneous, abo 20–30 microns in diameter and are almost ways birefringent: these are strongly remin cent of the "starch"-like bodies described Councilman in the kidneys of yellow fever a found by us often in the kidneys associat with any form of severe acute hepatitis acute yellow atrophy, viral or chemical T crystalline, yellowish green, spherical bodies of the same size as the amorphous ones, constantly birefringent, and have radial li so as to simulate the crystals of acetylat sulfathiazole (plates 137, 138) These bod resemble also leucine crystals and adenos phosphate, but their accurate identificati awaits further study. The crystals, as the amo phous bodies, are found in cases of seve acute hepatitis, and in jaundice secondary calculi or neoplasm obstructing the comm duct.

Any one, or a combination of the abo findings may be present with hepatic disea Obviously, the amount of dysfunction will va with the type and severity of the histolo change in the kidneys. In other words, me bile-staining of epithelium and scattered b casts need not cause significant renal dysfun

It is not always possible to know from t histologic sections alone what severity of ren dysfunction had existed As a rule, howev the more closely the over-all histologic pictu

approaches that of hemoglobinuric nephrosis—substituting bile casts for hemoglobin casts—the more easily can it be suspected that corresponding renal dysfunction had occurred.

### *Pathologic Physiology*

In view of the intimate association of hemoglobinuric nephrosis and other renal damage with disease of the liver as in carbon tetrachloride and mushroom poisoning, sulfonamide intoxication (Kuzma and Polley), and infarct of the liver, there can be no doubt of a pathogenetic relationship between hepatic disturbances and renal changes. What the precise mechanism is, remains to be clarified. It is a known fact, however, that an abnormal aminoaciduria may occur with severe damage of the liver, and that leucine, tyrosine, and other amino acids are excreted Experimentally, renal tubular damage can be produced with serine, cystine, lysine, arginine, aspartic acid, histidine, and tryptophane (Morehead et al , Cox et al , Newburgh and Marsh, Lillie). Whether or not such an aminoaciduria plays a role in the renal damage in humans is still to be proved Recently it has been postulated that the acutely damaged liver is vitally concerned with the maintenance of the balance of circulating vaso-excitatory and vaso-depressive substances, and that a disturbance in this balance causes renal dysfunction of the types noted in the hepato-renal syndrome

## SULFONAMIDES

### *Introduction*

The effect of the sulfonamides on the kidney constitutes the most frequent of the serious untoward responses to this important group of drugs The problem of establishing the basis for a given renal reaction in humans, however, is often hopelessly tangled by the large number of possibly related variables of which transfusions, shock, infections and accompanying allergies are the significant ones The problem is further complicated by the fact that each of these variables alone may be responsible for the types of inflammatory lesion also attributable to the sulfonamides. The following outline lists the renal lesions that are produced by sulfonamides

*Renal reactions to the sulfonamides:*

- Obstructive calcinosis
  - Intrarenal
  - Pelvic and ureteral
- Inflammatory
  - Nephrosis
    - Necrotizing nephrosis
    - Hemoglobinuric nephrosis
  - Interstitial nephritis
    - Diffuse
    - Focal
  - Acute glomerulonephritis
    - Diffuse
    - Focal
  - Acute necrotizing pyelitis
  - Periarteritis nodosa

The conditions listed above may occur individually or in combination. There is nothing diagnostic about most of these lesions Except in the obvious obstructive uropathies, it is usually the clue from the gratuitous presence of a few crystals of sulfonamides, certain distinctive granulomatous reactions, and a convincing clinical history of the administration of the drug and concomitant effects (for example, skin rash) that leads to the inferential conclusions concerning pathogenesis

### *Obstructive Calcinosis*

Obstructive calcinosis has been observed experimentally following the administration of prontosil, sulfapyridine (Gross et al , Antopol and Robinson, Van Dyke et al ), sulfathiazole (Van Dyke et al , Climenko and Wright), sulfamethylthiazole, sulfadiazine, and sulfaguanidine, concrements were not noted with sulfanilamide experimentally. The sulfapyridine produces obstructive concretions more commonly than sulfathiazole (Van Dyke et al )

Fig A *Distinctive hydropic vacuolization* seen especially in cholemic nephrosis of whatever cause and also in ulcerative colitis The evidence of degeneration in the nonvacuolated epithelial cells of the proximal tubules is also noted

Fig B *Bile casts* with degeneration of epithelium of the distal tubules are seen in this case of cholemic nephrosis

Fig C. *Bile casts in the distal nephron* with necrosis and desquamation of epithelial cells are seen (cholemic nephrosis).




(Legends on facing page)




FIG A. *Dense bile casts and crystals* (arrow) in distal nephron in a case of poisoning with carbon tetrachloride

FIG B *Cholemic nephrosis* (carbon tetrachloride) showing spherical crystals, possibly leucine (black), proteid cast in the distal tubule, oncotic as well as destructive vacuolization in the proximal tubules

FIG C *Cholemic nephrosis* following obstruction of common bile duct by a carcinoma of the head of the pancreas, with bile casts, anisotropic spherical crystals (possibly leucine) (arrows) and destruction of epithelium of distal tubules

parently of bile pigment, are in the epithelium.

# PLATE 135. NEPHROSIS OF PROXIMAL AND DISTAL NEPHRON: CARBON TETRACHLORIDE FAT NEPHROSIS (PROXIMAL COMPONENT)




FIG A *Basal vacuolization* formed by fat in cells of proximal convoluted tubules in a case of acute yellow atrophy due to carbon tetrachloride (A F I P Acc 104604)

FIG B *Sudan III stain* of kidney illustrated in figure A




FIG A *Hemoglobinuric nephrosis* (casts of hemoglobin in distal tubules) in a case of carbon tetrachloride poisoning

FIG B *Focal interstitial nephritis* with edema and inflammation in carbon tetrachloride poisoning

FIGS C AND D *Alkalotic calcification in distal convoluted tubules* resulting from the vomiting so common in carbon tetrachloride poisoning Figure D shows also one of the spherical crystals (arrow) often seen in association with acute hepatic degeneration

## PLATE 137. Nephrosis of Distal Nephron: Sulfonamides, Sulfapyridine Crystals

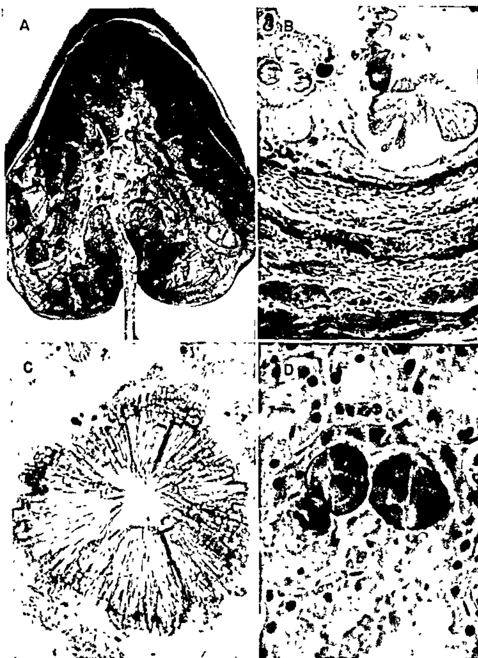
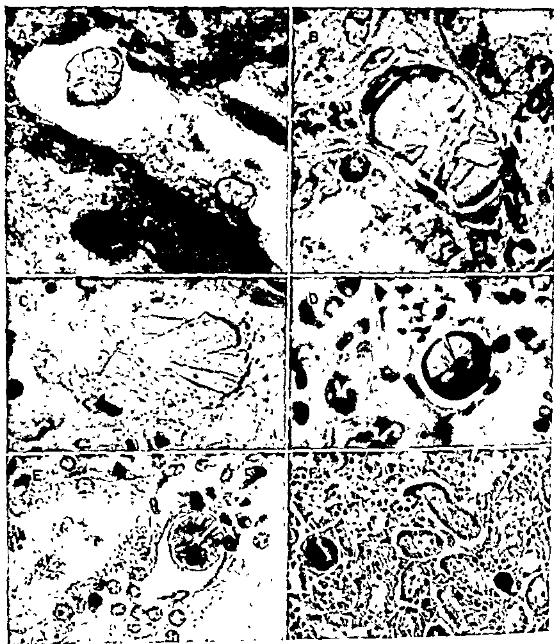



Fig. A *Sulfapyridine lithiasis* in renal pelvis and ureter. This patient manifested pain, hematuria, and dyspnea, but no renal insufficiency. (Case of Schifrin and Kelson.)

Figs. B and C *Acetylated sulfapyridine crystal*

Fig. D *Birefringent crystals*, possibly leucine, characteristic of acute hepatitis of many varieties. These crystals may be easily confused with the sulfonamides




FIGS A TO E. *Sulfadiazine crystals* in the lumens of distal convoluted tubules

FIG F *Leucine* (?) crystals in kidney associated with a large infarct of the liver They occur also in acute yellow atrophy caused by a variety of agents

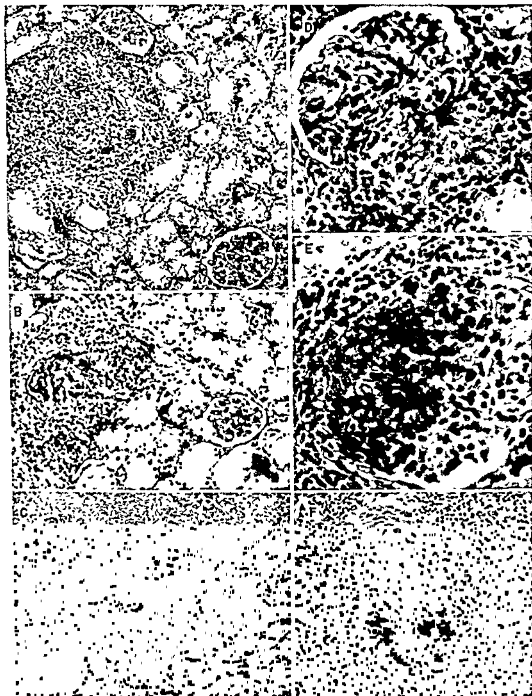



FIG A *Acute necrotizing glomerulitis* due to sulfathiazole Two normal glomeruli are included in the section

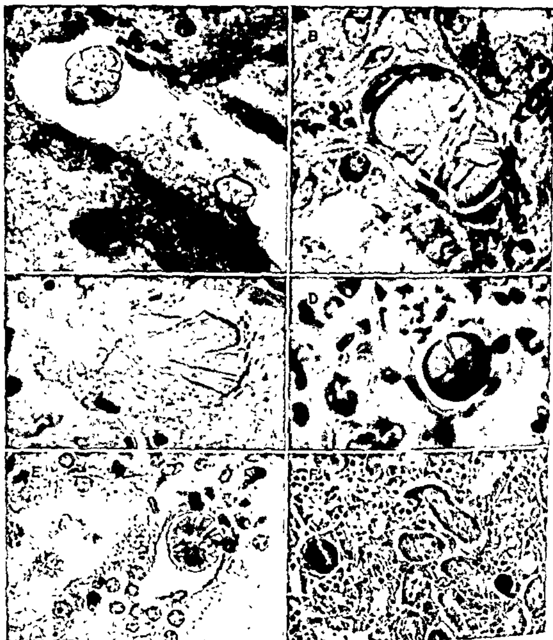
FIG B *Acute focal exudative glomerulitis and periglomerulitis* due to sulfathiazole

FIG C *Acute focal exudative glomerulitis and periglomerulitis* due to sulfathiazole

FIGS D AND E *Acute focal glomerulitis* (sulfathiazole) indistinguishable from focal endocarditic glomerulitis

FIG F. *Acute renal arcuate arteritis* due to sulfathiazole, indistinguishable from that of periarteritis nodosa.

## PLATE 138. Sulfadiazine Toxicity: Appearance of Crystals in Sections of Kidney




Figs A to E. *Sulfadiazine crystals* in the lumens of distal convoluted tubules

Fig F. *Leucine* (?) crystals in kidney associated with a large infarct of the liver They occur also in acute yellow atrophy caused by a variety of agents

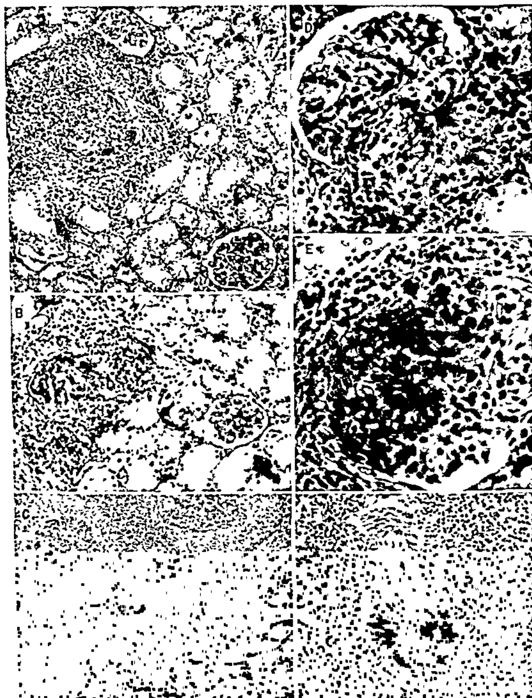


FIG A *Acute necrotizing glomerulitis* due to sulfathiazole Two normal glomeruli are included in the section

FIG B *Acute focal exudative glomerulitis and periglomerulitis* due to sulfathiazole

FIG C *Acute focal exudative glomerulitis and periglomerulitis* due to sulfathiazole

FIGS D AND E *Acute focal glomerulitis* (sulfathiazole) indistinguishable from focal endocarditic glomerulitis

FIG F *Acute renal arcuate arteritis* due to sulfathiazole, indistinguishable from that of periarteritis nodosa

presumably because of the relative insolubility of the actylated sulfapyridine of which the calculi are composed.

In humans, crystals of the various sulfonamides are found commonly within the parenchyma but obstructive concretions of sulfonamides, such as are illustrated in plate 137 A, are found relatively rarely in the pelvis or ureter. Some observers attribute the infrequency of this finding to the calculi having been washed out in the urine. Their disappearance by this route would hardly seem to be an adequate explanation to account for their rarity at autopsy. The conclusion is that extraparenchymal obstructive calcinosis from sulfonamides is an unusual complication.

*Intrarenal Calcinosis*

The intrarenal deposition of sulfonamide crystals is a common occurrence The crystals are noted frequently, notwithstanding the partial solution of the crystals that occurs in the process of preparation and staining of paraffin sections The crystals are found in the distal convoluted tubules (plate 138) and only exceptionally in the proximal convoluted tubules (plate 145 C) These crystals may be confused particularly with those seen in the kidney in association with acute hepatitis or hepatic necrosis (plate 137 D), and in some instances may indeed be those very crystals in view of the common association of liver damage in 37 per cent of cases of serious renal complications from sulfonamides (Kuzma and Polley) Sulfonamide crystals may also be mistaken for the crystals of calcium oxalate precipitated in the proximal tubules after the ingestion of ethylene glycol (antifreeze) The calcium deposits in the distal tubules as a result of alkalosis or metastatic calcification usually offer no serious differential diagnostic problem

Before concluding that intratubular crystals re responsible for renal insufficiency by obstruction of the tubular outflow, evidence of backpressure in the form of internal hydronephrosis (dilated tubules and Bowman's spaces) should be required In point of fact, such dilatation is rarely caused by intrarenal deposits of sulfonamides. In other words, renal shutdown in the presence of parenchymal crystals of sulfonamides is usually due to associated hemodynamic or inflammatory reactions rather than primarily to tubular obstruction

*Inflammatory Reaction to Sulfonamides*

*Nephrosis*

The renal reaction to the sulfonamides that is of most concern, both because of its frequency and its gravity, is hemoglobinuric nephrosis It may follow the administration of any of the sulfonamides There may be no difference in the clinical or histologic picture of hemoglobinuric nephrosis caused by the sulfonamides from that previously described and caused by incompatible transfusions and the many other agents or conditions. In some instances, a hint of a sulfonamide etiology is based on the finding of sulfa crystals, often embedded in irregular proteid casts in the distal convoluted tubules (plate 143 B). The presence of interstitial giant cell granulomas (plate 143 C, 144 A) is an additional suggestion of a reaction to sulfonamides Eosinophilic leukocytes within the interstitial infiltrate also is presumptive but far from conclusive evidence of an allergic reaction, possibly to sulfonamides.

Infrequently vacuolization, degenerative changes and actual necrosis of the epithelium of the proximal convoluted tubules occur after sulfathiazole therapy with as serious dysfunction as in hemoglobinuric nephrosis One such example is illustrated in plate 140 B, and appears to correspond to the description of another case (More et al ) in which sulfathiazole was used.

*Interstitial nephritis*

Acute diffuse interstitial nephritis of clinical and histologic types identical with those associated with various septic states occurs infrequently after sulfonamide therapy (plate 141). Of more distinctive histologic appearance, are the examples of focal granulomatous interstitial nephritis described by Lederer and Rosenblatt, as well as others, and characterized by giant cells, various mononuclear cells, eosinophilic and neutrophilic leukocytes, and necrosis These granulomas may occur in other organs including lungs and bone marrow. They are not a direct reaction to the sulfonamide




FIG A *Acute diffuse exudative glomerulonephritis* attributed to sulfapyridine The intense exudation of polymorphonuclear leukocytes is present in the periglomerular lymphatics as well as in the glomeruli themselves

FIG B *Proximal and distal tubular degeneration and regeneration* in reaction to sulfapyridine

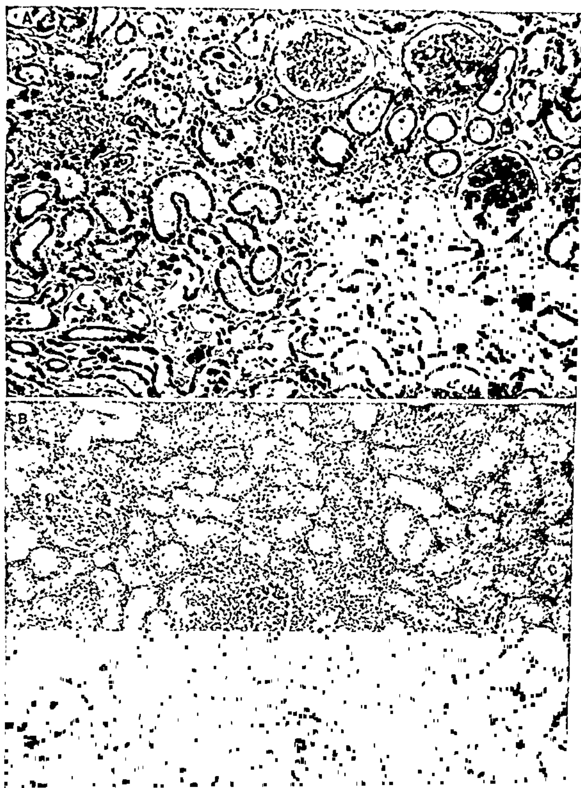



FIG A *Focal interstitial nephritis* with marked edema due to sulfathiazole

FIG B *Acute diffuse interstitial nephritis* due to sulfathiazole

crystals but apparently represent an allergic response

*Acute glomerulonephritis*

It is not generally appreciated that acute diffuse glomerulonephritis and acute focal glomerulonephritis may represent one of the responses to the sulfonamides This statement is made with the awareness, previously indicated, of the conflicting possibility that the glomerular reaction may be the result of the original infection for which the sulfonamide was given This possibility was taken into full account when the cases illusrated in plates 139 and 140 were chosen as examples of glomerulonephritis caused by sulfonamides The focal glomerulitis illustrated in plate 139 A is characterized by the same type of granulomatous nonbacterial inflammation that is present in the granulomatous interstitial nephritis, and in the granulomatous arteritis attributed to the sulfonamides or allergic responses (plate 237)

*Necrotizing pyelitis*

Acute hemorrhagic necrotizing calycitis, pyelitis, and ureteritis have been observed occasionally following sulfapyridine (Sadusk et al , Koletsky and King) and sulfathiazole therapy. The case illustrated in plate 147 with hemorrhagic necrotic pyelitis, and ureters obstructed by hemorrhagic exudate admixed with scattered crystals, followed treatment with sulfathiazole In one case (Katzenstein and Winternitz), the necrosis caused rupture of the pelvis.

*Periarteritis nodosa*

The emphasis placed by Rich on the role of sulfonamides in the production of vascular lesions indistinguishable from those of periarteritis nodosa has since led to at least a preliminary search of sulfonamide etiology in all cases of periarteritis nodosa The evidence is convincing that such lesions may follow the development of hypersensitivity to the sulfonamides with fatal results As mentioned, a peculiar form of necrotizing granulomatous arteritis (plate 237), not unlike the granulomatous reaction previously described, may be observed in patients with altered reactivity to sulfonamides.

*Summary of Renal Reaction to Sulfonamides*

With the increasing use of sulfonamides, evidence has been accumulated of a wide variety of forms of renal damage related directly to the use of these drugs. The types of change include.

1 acute focal or diffuse interstitial nephritis,
2 acute focal or diffuse glomerulonephritis,
3 hemoglobinuric nephrosis,
4 focal necrotizing nephrosis,
5 hemorrhagic necrotizing pyelitis,
6 necrotizing arteritis, and
7 the obstructive deposition of masses of crystals of the sulfonamides

There is no constant relationship between the amount of the drug administered and the severity of the renal damage, nor is there a relationship, necessarily, between the severity of the damage and the numbers of crystals observed in sections This latter impression is not altered by the fact that the crystals have a tendency to be dissolved both in the process of fixation with formalin and in the preparation of paraffin sections

The renal lesions may be associated with changes in other organs affected by the sulfonamides These include interstitial eosinophilic myocarditis, diffuse necrotizing arteritis simulating periarteritis nodosa, purulent granulomatous necrotic foci in the lungs, liver, spleen and bone marrow, acute yellow atrophy of the liver, a variety of other changes in the bone marrow, focal necrosis of lymph nodes, encephalomyelitis, and several types of cutaneous rashes On the other hand, isolated renal lesions do not preclude the possibility of sulfonamides being the offending agent The pathogenesis of sulfonamide toxicity remains to be clarified, but the evidence to date strongly suggests an allergic factor in which sulfa drugs play the part of haptenes

Attempts to prevent or minimize the precipitation of sulfonamide crystals and the formation of concrements have been made, not only by the alkalinization of the urine, and the dangerous and dubiously effective forcing of fluids, but also by the simultaneous use of




FIG A *Hemoglobinuric (lower nephron) nephrosis* due to sulfathiazole the epithelium of the collecting tubules containing the casts is not appreciably altered

FIG B *Tubular dilatation* in a case of hemoglobinuric nephrosis due to sulfathiazole This degree of dilatation is not common in hemoglobinuric nephrosis




FIG A *Thrombophlebitis* of arcuate vein in hemoglobinuric nephrosis due to sulfathiazole, a common finding in this condition

FIG B *Thrombophlebitis* in reaction to sulfathiazole The necrotic distal tubules containing the hyaline casts lie directly against the endothelium of the vein and thereby thrombosis is facilitated (Case of hemoglobinuric nephrosis)

FIG C *Sulfathiazole toxicity* with giant cell granuloma about a partially degenerated tubule containing a hyaline cast

mixtures of sulfonamides (Lehr). The thought behind such combinations of drugs is that they would preserve or even enhance the antibacterial action and at the same time inhibit the formation of crystals because of the diminished concentration of any one drug in the solution administered The criticism leveled at this procedure is that, while it may lessen the chances of the formation of crystalline precipitates, it may promote the tendency to allergic reactions by virtue of the exposure to multiple allergenic drugs This latter danger seems the far more important one to avoid.

### Poisoning from Hydroquinone-Pyrogallol (Photographic Developer)

The crystals used as a reducing agent in photographic developing fluid, and used also in the fur industry, have caused fatalities through accidental ingestion. In one instance, the crystals were mistaken for epsom salts; a tablespoonful was swallowed, and death ensued in 48 hours. The composition of the material is 80 per cent hydroquinone, 20 per cent *p*-methylaminophenol sulfate and pyrogallol. The pyrogallol (trihydric phenol, $C_6H_3(OH)_3$) is a well known destructive agent of red blood cells, and is employed for this property in the performance of routine chemical tests, and in the bacteriologic laboratory to create an anaerobic atmosphere. It converts hemoglobin into methemoglobin. Poisoning causes chills, vomiting, diarrhea, cyanosis, anemia, jaundice, circulatory collapse, oliguria and anuria, and death from the combined multiple effects usually in a few days.

The renal picture consists of the presence of hemolyzed blood throughout the nephron, from the very much dilated Bowman's space to the collecting tubules. These homogeneous casts of hemolyzed blood should be easily distinguished from the granular, heme casts by their thin, homogeneous, pale, and also serous appearance, as if the hemolyzed blood had been diluted and escaped into the urine, coloring pink whatever it contacted on its way No significant tubular degeneration or other noteworthy change is present (plate 131 A).

### von Gierke's Disease

The entity known as glycogen storage disease, hepatonephromegalia, glycogenemia, thesaurismosis glycogenica, or more commonly, von Gierke's disease, was first described by E. von Gierke in 1929. The disease occurs almost exclusively in infants, and the essential clinical findings are hepatomegaly, cardiomegaly, nephromegaly, flattened glucose tolerance curve, generally asymptomatic hypoglycemia and acetonuria. Cerebral symptoms have also been described (Kimmelstiel).

The same organs are not involved in each case and the degree of their involvement varies from case to case. To this extent, the signs and symptoms are different in the small number of cases thus far described. The essential histologic picture is that of glycogen disposition so excessive as to cause marked enlargement of the organs The liver may be enlarged three to four times and the kidneys to fully twice normal weight. In the liver, the glycogen is in the parenchymal cells; in the heart, the individual fibers may be enormously ballooned out into a network by the glycogen. Glycogenic enlargement of the myocardium may be focal and may present as a tumefaction which in the past has been mistaken occasionally for rhabdomyosarcoma (plate 148 C). In the kidney, the site of deposition of the glycogen is variously reported in any or all portions of the nephron including the glomerular tuft, Bowman's space, the parietal epithelium, the epithelium of the proximal, distal and collecting tubules, as well as the lumens of the tubules. In other words, the glycogen is not confined to the region of the loops of Henle as in diabetes mellitus nor are the vacuoles nearly as large as those of diabetes mellitus (plate 108 C, 148 A) The analysis of the kidneys in von Gierke's case by Schonheimer revealed them to contain 6 53 per cent of glycogen, whereas the maximum value found in the kidney in diabetes mellitus was 1 64 per cent (Popper and Wozasek) The glycogen deposits do not cause renal insufficiency Glycogen has been found also in the brain, in the endocrine glands, in muscles, in the pancreas and in blood vessels.

There is no evidence that the glycogen is



FIG A *Giant cell granulomas* about distal convoluted tubules in sulfathiazole toxicity

FIG B *Calcification of distal nephron* in a case of sulfathiazole toxicity in the absence of alkalosis



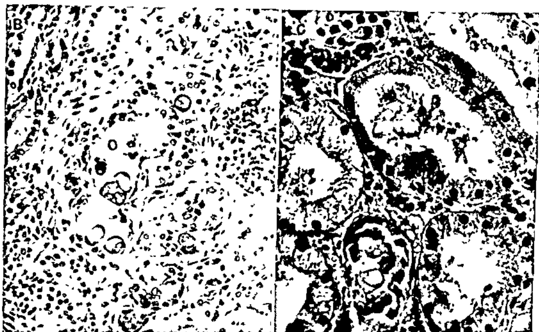




FIG A *Doubly refractile crystals* in kidney following oral administration of Sulfasuxidine The crystals of other sulfonamides are also doubly refractile Despite the relative lack of reabsorption of Sulfasuxidine, apparently a sufficient amount may be absorbed on occasion to produce the crystalline deposits in the kidney shown above

FIG B *Crystals in distal tubules* following use of sulfasuxidine

FIG C *Crystals in proximal convoluted tubules* following the use of Sulfasuxidine This patient was also given ascorbic acid, of which a theoretical intermediate product of metabolism is calcium oxalate

abnormal in composition or that there is a significant excess of it in the blood. Urinary amylase has been found increased in some cases. The supposition is that there is an enzymatic disorder of glycogenolysis at fault. Renal phosphatases, both acid and alkaline, show no abnormality (Wachstein) (plate 148 B).

## Multiple Myeloma

### Introduction

Although renal insufficiency is a common cause of death in patients with multiple myeloma (43 per cent according to Adams et al.), there is much difference of opinion as to exactly what renal lesions are present. In part the difficulty arises from the fact that multiple myeloma is a disease of the latter decades of life, in which age groups renal lesions occur (for example, arterial and arteriolar nephrosclerosis, pyelonephritis) that are independent of the myeloma. In addition, myelomatous disease of the vertebral column may involve the spinal cord so as to lead to a "cord bladder" and consequent pyelonephritis. Moreover, about 6 per cent of patients with myeloma develop amyloidosis. As a rule, however, the amyloidosis is of the atypical type or "para-amyloidosis" in which the amyloidotic change is found in unusual sites, such as tongue, heart, skin, bone and joints rather than in the liver, spleen and kidneys. Therefore, only a very small percentage of cases of multiple myeloma have renal failure as a result of renal amyloidosis. The hyperglobulinemia which is so commonly present in multiple myeloma is probably pathogenetically related to the amyloidosis. Finally there are rare cases in which the kidney is the seat of actual myelomatous deposits (plate 152 E, 331). These infiltrations are focal and may be dismissed as a cause of renal insufficiency. There remains, nonetheless, a lesion directly responsible for renal insufficiency; this lesion has been termed *myeloma nephrosis* and, according to Šikl, was first described by von Decastello in 1909.

### Bence-Jones Protein

The precise nature and source of the Bence-Jones protein or proteose are not clear despite extensive investigations since the time of its recognition in 1847. The molecular weight of the Bence-Jones protein is about 25,000 to 30,000 as against 68,000 for albumin and 150,000 for globulin. Its molecule therefore is able to pass the glomerular filter, probably without causing injury to the glomerular capillaries or requiring them to be abnormally permeable. It has many properties in common with serum proteins, especially pseudoglobulins, including its solubility in water, its precipitation by 50 per cent ammonium sulfate and its similar refractive index and absorption spectra. The phosphorus content of Bence-Jones protein is low and its content of aromatic amino acids is high (Hewitt). The Bence-Jones protein coagulates at a lower temperature than either albumin or globulin and on further heating is redissolved, to reappear on cooling. An alkaline or strongly acid solution prevents coagulation. It gives a purple biuret reaction unlike the pink of proteoses (Bewley). It has antigenic properties and immune sera can be prepared which differentiate it from other proteins. Bence-Jones protein does not pass through a dialyzing membrane as do albumin and proteoses (Miller and Baetzer). The Bence-Jones proteins from different cases may have variable properties according to Hewitt.

Bence-Jones proteinemia occurs in about 70 to 80 per cent of cases of multiple myeloma and is usually associated with hyperglobulinemia and inconstantly present proteinuria. The evidence points to the myelomatous cells as the source of the protein, and yet there is no correlation between the level of Bence-Jones proteinemia and the amount of tumor present. Bence-Jones proteinemia is said to occur rarely in the absence of myeloma. Boggs and Guthrie long ago reported its presence in a case of carcinoma of the breast with osseous metastases and cited several other reports. Such instances, however, are sufficiently infrequent to make the finding of Bence-Jones proteinemia or proteinuria practically pathognomonic of multiple myeloma. Hyperglobulinemia as high as 15.5 Gm. per cent is on record.

### Pathology

#### Gross appearance

The kidneys of myeloma nephrosis are slightly decreased in size, but the surfaces

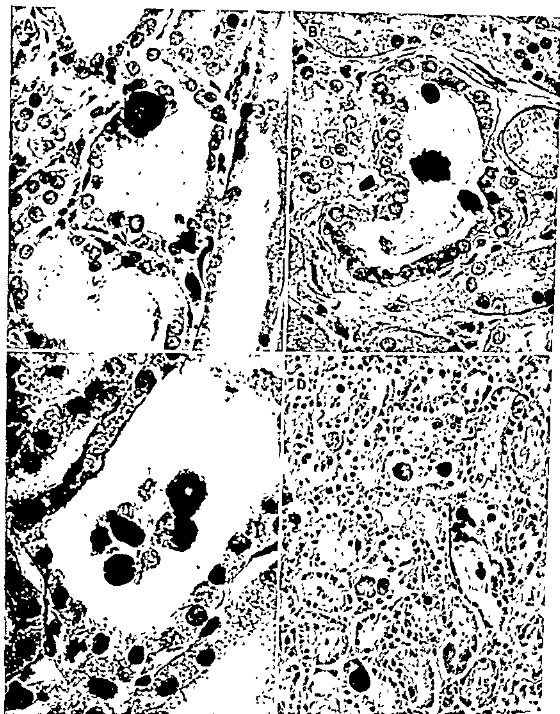



FIG A. *Sulfathiazole crystal* with hyaline cast in distal convoluted tubule

FIG. B. *Calcified bodies* in distal convoluted tubules in lower nephron nephrosis of crush syndrome in a patient without sulfonamides

FIGS C AND D *Greenish-yellow crystals* similar to crystals of acetylated sulfadiazine in distal convoluted tubules in yellow fever. These crystals are probably leucine.

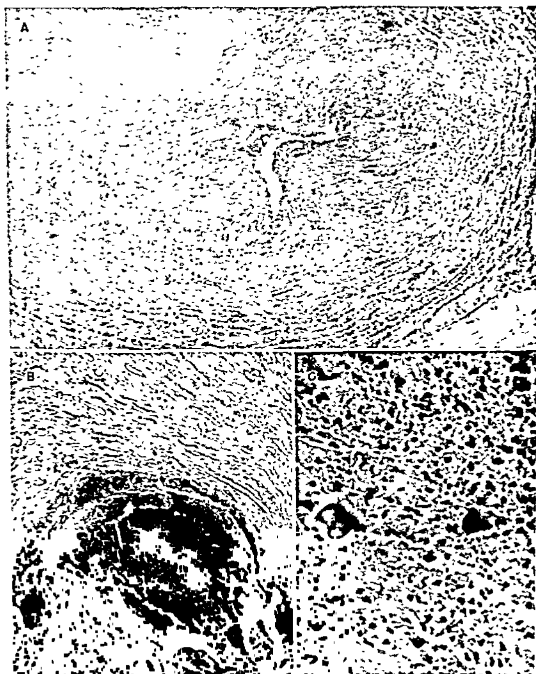



FIG A. *Sulfathiazole ureteritis* with purulent inflammation about crystals of acetylated sulfathiazole, shown in higher magnification in figures B and C

FIG B *Hemorrhagic calycitis* due to sulfathiazole

FIG C *Crystals of acetylated* sulfathiazole in midst of obstructing purulent exudate in ureter

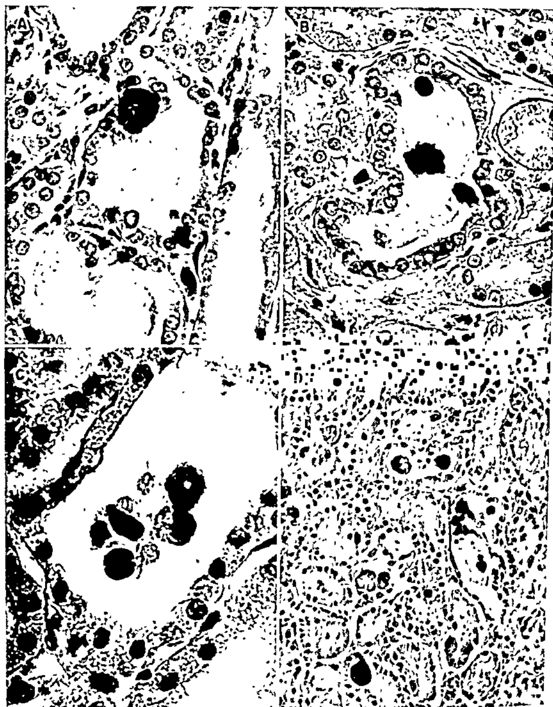



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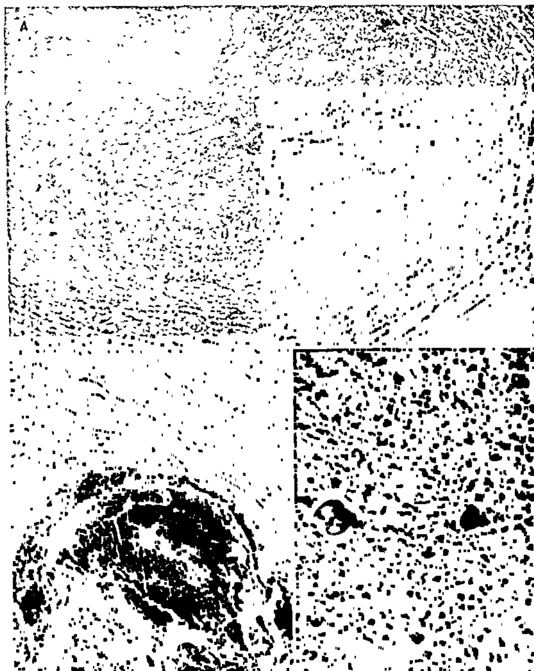



FIG A *Sulfathiazole ureteritis* with purulent inflammation about crystals of acetylated sulfathiazole, shown in higher magnification in figures B and C

FIG B *Hemorrhagic calycitis* due to sulfathiazole

FIG C *Crystals of acetylated* sulfathiazole in midst of obstructing purulent exudate in ureter

tend to be smooth and on sectioning, are pale and wavy (plate 149 A).

*Histologic appearance*

There are four principal histologic features of myeloma nephrosis: (1) the casts, (2) the tubular epithelial reaction about the casts, (3) the tubular atrophy and (4) the parenchymal nephrocalcinosis ("metastatic calcification").

*Casts* The casts are localized to the distal portion of the nephron, chiefly to the distal convoluted tubules They are uncommonly in the limbs and loops of Henle. They are brightly acidophilic, dense, and occasionally in concentric rings of variable thickness (plate 149 B, C) The central portions of the casts tend to be fragmented, granular, pocked with small locules and unevenly calcified Distorted, desquamated epithelial cells and a few leukocytes may be included More often the casts are not lamellated but are composed of a similar dense material staining irregularly pink with eosin but artefactitiously broken apart into several segments in the manner of glomerular amyloid The casts do not take the metachromatic stains for amyloid

*Crystals* In rare instances, *crystals* are found in the tubules, usually in the distal convoluted tubules, free or in association with the casts, and infrequently in the loops and limbs of Henle These crystals are short and long, needle shaped, hexagonal, prismatic, rhomboid and arranged singly or in packets (plate 152). They are not birefringent and as a rule are stained with the acidophilic dyes although some do not take the stain According to Šikl, this observation was first reported verbally by Lohlein in 1913 and published by him eight years later Fourteen cases have been reported to date (Šikl), no such finding was noted in 18 of our own cases Professor Šikl was kind enough to let us have some of his material for study. No special stains are required for the demonstration of these crystals. In 6 of the reported cases, Bence-Jones proteinuria was present; 2 are regarded as negative and in the remaining 6, the information is not available In 5 of these latter cases, the bone marrow was not examined or details are altogether lacking, a sixth case was *reported as a leukemic lymphadenosis*. Those cases with Bence-Jones proteinuria and *renal crystals* were in cases of plasmocytic *myeloma*.

The crystals are stated to resemble the Bence-Jones protein that has been crystallized *in vitro although they* are not dissimilar in shape to the crystals of *hemoglobin (plate 126 D)* By their distribution and morphology, the crystals seem not to have been deposited in the casts but to have risen from them. They are present also in the renal epithelium of proximal convoluted tubules, an observation first made by Apitz (plate 152 D). Some of the crystals closely resemble the plasmocellular crystalline inclusions (Russell bodies) so prominent in the infiltrate of rhinoscleroma. Similar crystals have been observed in the cytoplasm of myelomatous plasma cells (Glaus) and in other organs than the kidney (Šikl, Neumann).

*Tubular epithelial reaction* One of the almost specific identifying features of the myeloma kidney is the syncytium of epithelial cells about the dense casts These collections of cells are commonly referred to as foreign body giant cells provoked by the irritative casts. However, detailed studies of the transitional phases in their formation suggest that they represent a fusion of the tubular epithelium about the casts These syncytia are always intraluminal. Usually, the adjacent single tubular cells are

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Fig A *Von Gierke's disease* Kidney from a ten week old infant with von Gierke's disease The glycogen is seen as fine black granules in the distal convoluted tubules, in the wall of an arteriole, and in the cells of the glomerulus The proximal convoluted tubules did not contain glycogen in this case (Best's carmine stain) Contrast these fine vacuoles with the large vacuoles of glycogen in diabetes mellitus (plate 108) (Histologic slide obtained through courtesy of Dr M Wachstein.)

Fig B *Alkaline phosphatase* in the kidney of von Gierke's disease illustrated in figure A There is no abnormality of distribution of either alkaline or acid phosphatase

Fig. C *Heart in von Gierke's disease.* The vacuoles within the myocardial fibers contain glycogen From case illustrated in figure A




(Legends on facing page)




Fig A *Kidney from multiple myeloma* showing no distinctive gross features except, perhaps, for firm waxy appearance

Fig B *Dense laminated casts* with soft cores in a case of multiple myeloma with Bence-Jones proteinuria




FIG. A *Kidney of multiple myeloma with Bence-Jones proteinuria* showing minimal involvem in the form of dense casts with associated alteration of epithelial cells and slight interstitial fibro

FIG. B *Centrally softened cast* of multiple myeloma with peripheral syncytium of tubular epithelial cells in a case with Bence Jones proteinuria

FIG. C *Renal metastatic calcification* o specific variety, in a case of extensive myel

FIG. D *Centrally calcified casts* of kidney in a case of multiple myeloma

FIG. E *Metastatic calcification* in a char cast of myeloma kidney showing giant cells of tubular epithelium

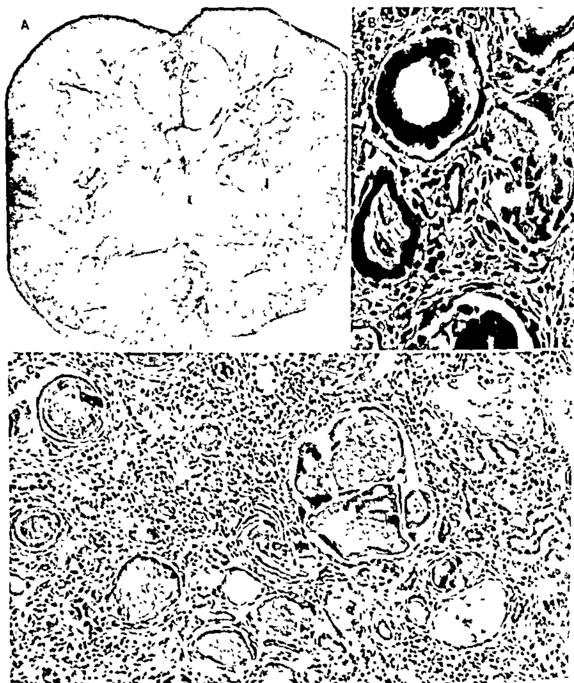



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FIG C [illegible] granular soft [illegible] tually [illegible]




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Fig C *Renal metastatic calcification* of a non-specific variety, in a case of extensive myelomatosis

Fig D *Centrally calcified casts* of kidney in a case of multiple myeloma

Fig E *Metastatic calcification* in a characteristic cast of myeloma kidney showing giant cells made up of tubular epithelium

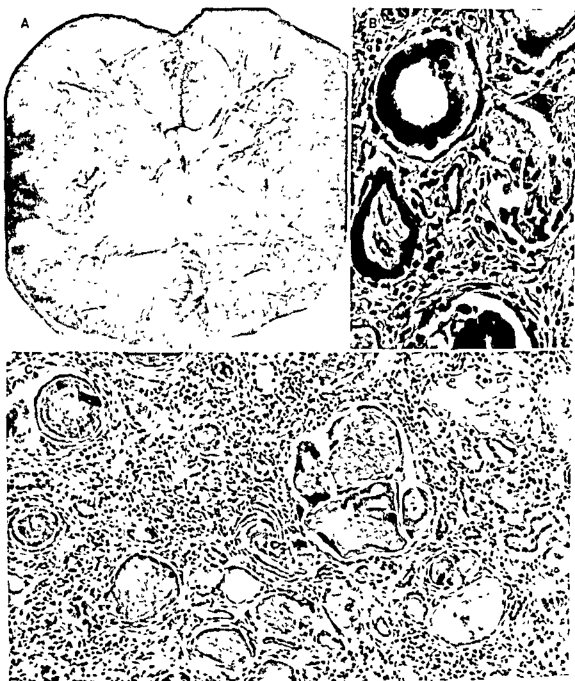



FIG A *Kidney from multiple myeloma* showing o distinctive gross features except, perhaps, for in waxy appearance

FIG B *Dense laminated casts* with soft cores in a case of multiple myeloma with Bence-Jones proteinuria

FIG C *Characteristic picture of kidney in multiple myeloma* showing laminated casts with granular soft centers and giant cells in various stages of development These giant cells appear to be actually a syncytium of tubular epithelial cells rather than foreign body giant cells.




FIG A *Kidney of multiple myeloma with Bence-Jones proteinuria* showing minimal involvement in the form of dense casts with associated alteration of epithelial cells and slight interstitial fibrosis

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FIG E *Metastatic calcification* in a characteristic cast of myeloma kidney showing giant cells made up of tubular epithelium

of similar quality and show degenerative as well as regenerative features. The epithelial cells of the proximal portions of the involved tubules may also show degenerative and regenerative changes in the absence of casts. In this connection, it should be mentioned again that syncytial masses of fused epithelial cells are found commonly in normal kidneys of patients over 40 years of age (plate 151 C) These should not be confused with the epithelial syncytium about casts in myeloma kidneys Giant cells form also about calcific deposits (plate 151 D), and about foreign bodies, for example, sulfonamide crystals (plate 151 B), and of course as parts of various tubercles These should offer no diagnostic difficulty

*Tubular atrophy* The tubular atrophy in myeloma nephrosis has been attributed by some observers (Perla and Hutner) to the effects of arteriosclerosis, but there can be no doubt that tubular atrophy occurs also on another, more specific basis The frequent disparity between the marked degree of tubular atrophy and the relatively early stages of arteriosclerosis by itself suggests the incomplete dependence In cases in which the vascular sclerosis is appreciable, corresponding tubular change may naturally be expected, and usually the degree of correlation can be made with reasonable accuracy However, the bulk of the tubular atrophy of the myeloma kidney is independent of vascular sclerosis and is constantly associated with dense obstructive casts. There is also moderate interstitial fibrosis with slight inflammatory infiltrate Despite extensive tubular change, the appertaining glomeruli may in some cases show a complete absence of sclerotic atrophy, such atrophy would be expected if the pathogenesis were on the basis of vascular sclerosis (plate 149 C) The glomeruli in these instances are free of the fibrotic change usually associated with hydronephrotic atrophy except for mild to moderate thickening of Bowman's capsule It is of additional concern that the tubular atrophy attributed to the proteid casts does not cause dilatation of tubular lumens and Bowman's spaces proximally, but, instead, the lumens are contracted Plugging of tubules obviously may cause hydronephrotic atrophy, just as complete obstruction of the ureter may under certain circumstances cause renal atrophy without pelvic dilatation.

*Parenchymal nephrocalcinosis* ("metastatic" calcification): Parenchymal nephrocalcinosis ("metastatic" calcification) is a common finding in the kidneys of patients with multiple myeloma The location of calcific deposits in metastatic calcification happens to be the same as that chiefly involved in the other tubular changes of myeloma nephrosis Hence, it is not surprising that the casts and the tubular epithelium about the casts may be calcified. However, the possibility that the proteid casts of myeloma have an added affinity for calcium cannot be altogether excluded, especially in view of the focal granules of calcium observed in their centers, in the absence of tubular epithelial calcification The metastatic calcification is a consequence principally of the lytic myelomatous lesions of bone, although often no direct correlation obtains between the extent of the osseous lesions and the renal calcification The renal insufficiency may contribute to the calcification by its effects on the parathyroid glands and the resultant secondary hyperparathyroidism

*Glomeruli*: No specific glomerular changes occur in cases of multiple myeloma There is often found a low-grade diffuse thickening of glomerular capillaries but this is quite nonspecific and is of the type seen, for example, in atrophic kidneys of chronic pyelonephritis or hydronephrosis In 1935, Foord observed what were considered inspissated plugs of protein in the glomerular capillaries in a case of multiple myeloma The renal insufficiency in this case was attributed to glomerular obstruction by the capillary plugs, the formation of which was believed to be related to the hyperproteinemia Data on the level of the proteinemia, however, are not given and studies of the urine for Bence-Jones protein were not done The description of the glomerular lesions is reminiscent of those seen occasionally in shock and dehydration and illustrated in plates 255 and 256 Actually, the patient just referred to did have a hemorrhagic diathesis with a marked anemia, and required transfusions This lesion, in our

## PLATE 151. Nephrosis of Distal Nephron: Multiple Myeloma (Differential Diagnosis of Casts)




Fig A *Inspissated casts and syncytia of tubular epithelial cells* in a case of chronic glomerulonephritis in a 6 year old This precise formation is rare outside of cases of myeloma

Fig B *Giant cells provoked by crystals* of acetylated sulfathiazole

Fig C *Syncytial proximal tubular epithelium* common as a finding after the fourth decade

Fig D *Reactive giant cell* to a calcium cast in a case of nephrocalcinosis secondary to osseous metastases This reaction is unusual in this condition

experience, is a terminal phenomenon and should be dissociated from the specific lesions of multiple myeloma

*Summary*

In summary, for all practical purposes, the specific diagnosis of multiple myeloma may be made with considerable assurance on the basis of a properly weighed integration of the type of histologic changes herein described It is plain that these changes may occur in the absence of renal insufficiency when they are not widespread, when they are extensive, they lead to progressive renal insufficiency and even to anuria (Holman) They are the preponderant cause of renal dysfunction in patients with multiple myeloma

The correlation of myeloma nephrosis with Bence-Jones proteinuria is probably much greater than the published reports indicate Undoubtedly the reason concerns the technical inadequacy of the performance of the tests for Bence-Jones proteinuria, the use of urine that has been at room temperature, or the insufficient number of determinations made, in view of the known intermittency of Bence-Jones proteinuria The many pitfalls are detailed in the report by Jacobson and Wilner There does not seem to be a correlation between the total level of blood proteins or the degree of proteinuria in multiple myeloma, and the extent or incidence of myeloma nephrosis or renal dysfunction, nor is the renal lesion of myeloma nephrosis found in other diseases with hyperglobulinemia, such as kala-azar, Boeck's sarcoid and disseminated lupus erythematosus Experimentally, there is a sharp discrepancy in the reports as to the histologic effects on the kidney of the administration of Bence-Jones protein to normal animals, McMahan and Magnus-Levy describe prominent tubular changes as opposed to the essentially negative findings of Forbus, Perlzweig and Parfentjev The study of renal function in patients with myeloma, by the use of clearance tests, yielded altogether unsatisfactory results (Armstrong).

## Gout

*Introduction*

There exists considerable confusion regarding the renal pathology of gout. The "gout kidney" is commonly spoken of, but, to different people, it may connote glomerulonephritis, arteriosclerosis, interstitial nephritis, a kidney with multiple small cysts, urate deposits in various locations, pyelonephritis, or combinations of these lesions. Actually, there is a specific lesion in gout, but it appears not to be the one generally in mind when the "gout kidney" is mentioned.

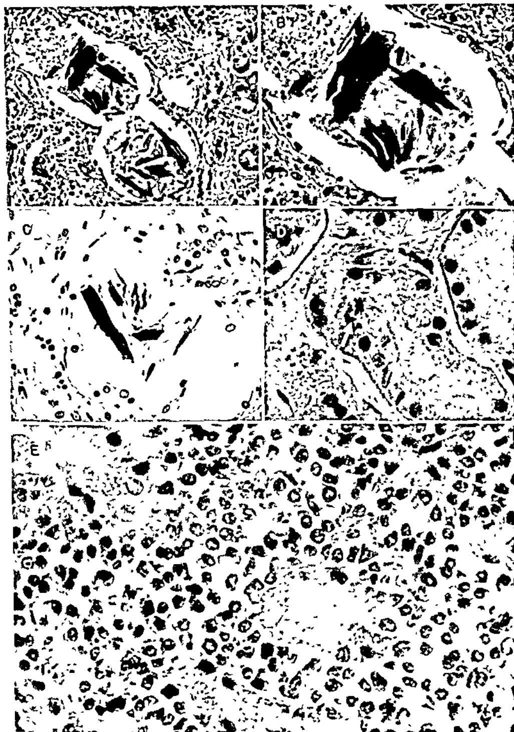
*Pathology*

The lesion of gout is made specific by the presence of sodium acid urate crystals primarily in the lumens of the collecting tubules, but with extension into the interstitial tissue, particularly of the lower portions of the pyramids The tubular epithelium about the casts of the crystals may be entirely destroyed (plates 153, 154 A) and their localization thereby missed These crystals which are found in the great majority of cases of gout, are easily recognized by their long, slender shape (or by the shape of the mold from which they have been dissolved in paraffin sections), by their disposition in sheaves, by their radial arrangement, and by the foreign body giant cells about their periphery in association with relatively little lymphocytic or histiocytic reaction The crystals of gout differ in appearance from those of the "uric acid infarcts" of children, which are presumed to be ammonium rather than sodium urate The urate crystals isolated from tophi are birefringent, but the crystals originally birefringent, are usually dissolved in paraffin sections of the kidney. Some of the

FIGS A, B AND C *Crystals of Bence-Jones protein* within tubules, from a case of multiple myeloma (Histologic slide obtained through the courtesy of Prof H Sikl of Prague)

FIG D *Crystals of Bence-Jones protein* within epithelial cells of proximal convoluted tubules (arrow)

FIG E *Myelomatous* (or myelosarcomatous) growth within renal parenchyma from a case of multiple myeloma, plasma cell type




(Legends on facing page)

experience, is a terminal phenomenon and should be dissociated from the specific lesions of multiple myeloma

### *Summary*

In summary, for all practical purposes, the specific diagnosis of multiple myeloma may be made with considerable assurance on the basis of a properly weighed integration of the type of histologic changes herein described It *is plain that these changes may occur in the* absence of renal insufficiency when they are not widespread, when they are extensive, they lead to progressive renal insufficiency and even to anuria (Holman) They are the *preponderant* cause of renal dysfunction in patients with multiple myeloma

The correlation of myeloma nephrosis with Bence-Jones proteinuria is probably much greater than the published reports indicate Undoubtedly the reason concerns the technical inadequacy of the performance of the tests for Bence-Jones proteinuria, the use of urine that has been at room temperature, or the insufficient number of determinations made, in view of the known intermittency of Bence-Jones proteinuria The many pitfalls are detailed in *the report by Jacobson and Wilner There does* not seem to be a correlation between the total level of blood proteins or the degree of proteinuria in multiple myeloma, and the extent or incidence of myeloma nephrosis or renal dysfunction, nor is the renal lesion of myeloma nephrosis found in other diseases with hyperglobulinemia, such as kala-azar, Boeck's sarcoid and disseminated lupus erythematosus Experimentally, there is a sharp discrepancy in the reports as to the histologic effects on the kidney of the administration of Bence-Jones protein to normal animals, McMahan and Magnus-Levy *describe prominent tubular* changes as opposed to the essentially negative findings of Forbus, Perlzweig and Parfentjev The study of renal function in patients with myeloma, by the use of clearance tests, yielded altogether unsatisfactory results (Armstrong)

## Gout

### *Introduction*

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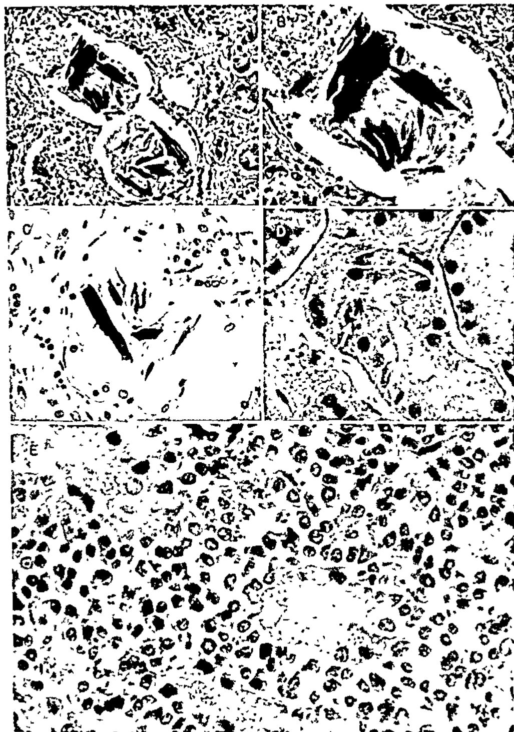
### *Pathology*

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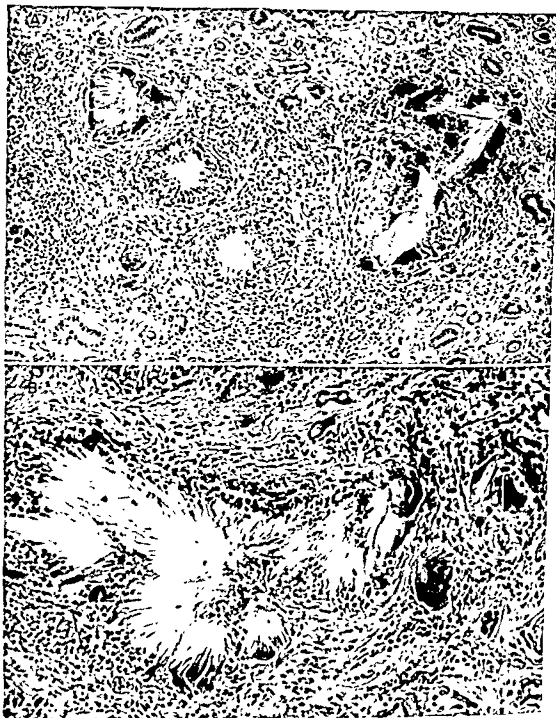


FIG A *Nephrosis of gout* with foci of sodium acid urate crystals and giant cells within the col- ... seen under ... [illegible] ... ally dissolved in the preparation of paraffin sections

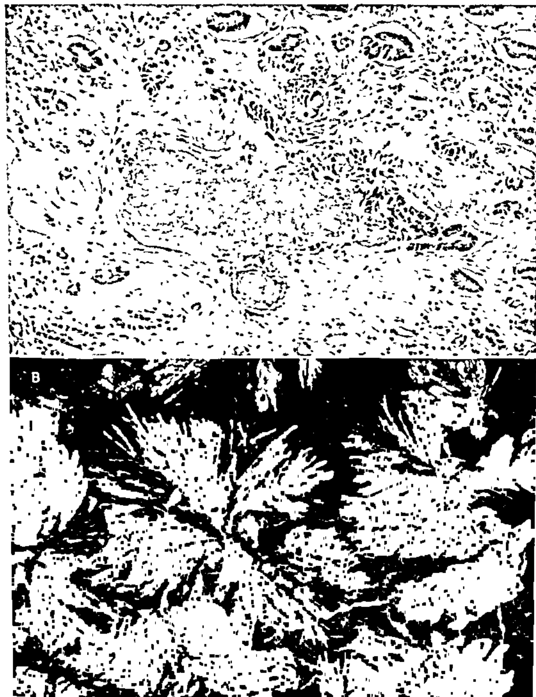



FIG. A. *Gout.* A cast of sodium acid urate crystals in a collecting tubule in which portions of the lining epithelium are still present.

FIG. B. *Gout. Birefringent* sodium acid urate crystals.



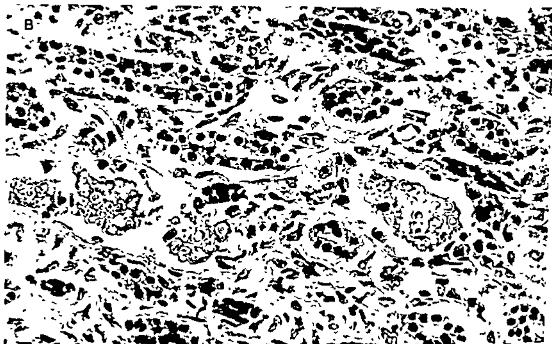




FIG A *Uric acid "infarcts"* in the kidney of a newborn infant The uric acid is present in the light colored streaked portions of the pyramids

FIG B *Isotropic uric acid crystals* in lumens of collecting tubules Similar crystals may be seen occasionally in treated cases of leukemia Ammonium urate is said also to be present

crystals may become ground into an amorphous urate dust (plate 154 A).

Such crystalline deposits are rarely responsible for renal insufficiency. The renal damage that is commonly present in kidneys of gouty patients are those judged to be incidental to the obesity, hypertension and age which characterize such patients. Of 55 patients with gout (average age 52 years), 17 had renal insufficiency (Schnitker and Richter). In other words, the resulting increased but nonspecific tendency to develop arterial and arteriolar nephrosclerosis would seem to be responsible for much of the renal damage erroneously attributed directly to gout. In this connection it is of interest to note Addis' view that gout should be suspected in patients with "long continued uremia of years' duration." He finds that these patients are all males without the usual signs of gout and generally are younger than those with classical gout. He refers to the condition in these patients as "secondary gout," attributing the rise in uric acid level in the blood not to faulty purine metabolism but to the consequence of inadequate amounts of effectively functioning renal tissue.

Although the chief intent of this section is to emphasize that the basis for the renal dysfunction in patients with gout is not the specific effect of the abnormal metabolism of uric acid, it would be incorrect to conclude that deposits in the kidney are never detrimental. The masses of urate crystals collect in the apices of the pyramids (plates 153, 154 A) which are critical bottlenecks in the urinary outflow. If a sufficient number of the ducts of Bellini are obstructed, renal function is compromised just as it occasionally is when calcium deposits occlude the outflow at this same site. Fortunately, such extensive blockage is rare. In isolated instances, however, the stasis produced in the collecting tubules clogged by urate crystals may lead to a superimposed localization of pyogenic organisms with the subsequent development of acute pyelonephritis (Brown and Mallory). The acute pyelonephritis may lead to immediate renal failure, or repeated attritive episodes of acute pyelonephritis may occur in these kidneys made vulnerable by the obstructive packets of crystals until finally insufficient renal tissue remains. In most instances of renal failure in patients with gout, the specific, obstructive, pyelonephritic element caused by the urates is merely one of several factors in the renal embarrassment, associated vascular disease of the kidney is one of the major accessory components.

### Uric Acid "Infarcts"

The term uric acid "*infarcts*" is really a loose designation referring to the golden yellow, fairly sharply defined wedge located in the papillae of the renal medulla (plate 155 A). These lesions are not actually infarcts but merely the focal collections of uric acid crystals in the terminal collecting tubules (plate 155 B). Such masses of crystals appear to occur when rapid destruction of nuclei takes place as in leukemia, in occasional infections, or, normally, in the newborn. It has been stated that in the latter physiologic state, there is an inadequate supply of the enzyme urease available for the need of the immediate postnatal period. No renal dysfunction has been attributed to the uric acid infarcts.

The collecting tubules occupying the apex of the pyramids are filled with spherical, sharply rimmed, laminated, acidophilic masses of uric acid crystals. The crystals are about 10 to 20 microns in diameter and are not birefringent, unlike those of gout. These crystals, along with granular protein precipitate and desquamated tubular epithelium, form casts. From the manner of denudation of the collecting tubules, it appears that they are the source of the epithelial cells within the uric acid casts. Evidence of nuclear reaction in the form of irregularity and hyperchromatism in these epithelial cells indicates that the casts are irritative. No significant dilatation is present in the portions of the nephron proximal to the casts nor is there any interstitial inflammation.

### References


*Osmotic Nephrosis*

Anderson, W. A. D. Sucrose nephrosis and other types of renal tubular injuries. South. M. J. 34: 257-263, 1941.

Baxter, J. H., and Cotzias, G. C. Effects of proteinuria on the kidney. Proteinuria, renal enlargement, and renal injury consequent on protracted parenteral administration of protein

solutions in rats. J. Exper. Med 89: 643-668, 1949

CHASIS, H., RANGES, H. A., GOLDRING, W., AND SMITH, H. W. Control of renal blood flow and glomerular filtration in normal man. J. Clin. Invest. 17: 683-697, 1938

HELMHOLZ, H. F. Renal changes in the rabbit resulting from intravenous injections of hypertonic solution of sucrose. J. Pediat. 3: 144-157, 1933

HEYMANN, W., AND HARTMAN, M. E.: Hyperlipemia following intravenous infusion of hypertonic solution of sucrose. Am. J. Dis. Child 75: 68-75, 1948

JACKSON, H., DICKERSON, D., AND GRENTHER, A. The reduction of intracranial pressure in cerebral injury by the intravenous injection of hypertonic sucrose solution. Ann. Surg. 106: 161-168, 1937

JAFFÉ, R. H., AND STERNBERG, H. Über die vakuolare Nierendegeneration bei chronischer Ruhr. Virchow's Arch. f. path. Anat. 227: 313-319, 1919-20

JENSEN, E. J., BAGGENSTOSS, A. H., AND BARGEN, J. A. Renal lesions associated with ulcerative colitis. Am. J. M. Sc. 219: 281-290, 1950

KEITH, N. M., WAKEFIELD, E. G., AND POWER, M. H. The excretion and utilization of sucrose when injected intravenously in man. Am. J. Physiol. 101: 63, 1932

KULKA, J. P., PEARSON, C. M., AND ROBBINS, S. L. A distinctive vacuolar nephropathy associated with intestinal disease. Am. J. Path. 26: 349-377, 1950

LAMY, H., MAYER, A., AND RATHERY, F. Modifications histologiques du rein au cours de l'élimination de l'eau et des cristalloïdes. J. de physiol et de path. gén. 8, 624-634, 1906

LINDBERG, H. A., WALD, M. H., AND BARKER, M. H. Renal changes following administration of hypertonic solutions. Arch. Int. Med. 63: 907-918, 1939

MURPHY, F. D., HERSHBERG, R. A., AND KATZ, A. M. The effect of intravenous injections of sucrose solution (50%) on the cerebrospinal fluid pressure, the blood pressure, and the clinical course in cases of chronic hypertension. Am. J. M. Sc. 192: 510-517, 1936

SMITH, H. W. Excretion of non metabolized sugars in dogfish, dog and man. Chapter V in Berglund, H., and Medes, G., The Kidney in Health and Disease. Philadelphia, Lea and Febiger, 1935

WILMER, H. A. The mechanism of sucrose damage of the kidney tubules. Am. J. Physiol. 141: 431-438, 1944

*Hyaline Granule Nephrosis*

ADDIS, T. Glomerular Nephritis. New York, Macmillan, 1948

ALLEN, A. C. in Proceedings of the 13th Seminar of the A.S.C.P. (with B. Lucké), 1947, p. 12-13. Published by Armed Forces Institute of Pathology

OLIVER, J. The structure of the metabolic process in the nephron. J. Mt. Sinai Hosp. 15: 175-222, 1948-1949

OPIE, E. L.: Cytochondria of normal cells, of tumor cells, and of cells with various injuries. J. Exper. Med. 86: 45-54, 1947.

—— The effect of injury by toxic agents upon osmotic pressure maintained by cells of liver and kidney. J. Exper. Med. 91: 285-294, 1950

RICHARDS, A. N. Croonian Lecture, processes of urine formation. Proc. Roy. Soc. London 126, 398-432, 1938

RATHER, L. J.[a] Renal athrocytosis and intracellular digestion of intraperitoneally injected hemoglobin in rats. J. Exper. Med. 87. 163-174, 1948

——[b] On the problem of renal tubular resorption of protein. Stanford Bull. 6. 117-125, 1948

SULTANA, H. The permeability of the renal glomeruli of several mammalian species to labeled proteins. Am. J. Path. 23: 255-268, 1947

SUZUKI, T. Zur Morphologie der Nierensekretion. Jena, Gustav Fischer, 1912

TERBRÜGGEN, A. Über das Vorkommen hyaliner Tropfen in der Niere in Abhängigkeit vom Auftreten korperfremden Eiweiss. Beitr. z. path. Anat. u. z. allg. Path. 86, 235-272, 1931

VOLHARD, F. AND FAHR, TH. Die Brightische Nierenkrankheit, Klinik, Pathologie und Atlas. Berlin, J. Springer, 1914

WEARN, J. T., AND RICHARDS, A. N. Observations on the composition of the glomerular filtrate with particular reference to the problem of reabsorption in the renal tubules. Am. J. Physiol. 71: 209-227, 1924

YUILE, C. L., STEINMAN, J. F., HAHN, P. F., AND CLARK, W. F. The tubular factor in renal hemoglobin excretion. J. Exper. Med. 74: 197-202, 1941

*Mercury Nephrosis*

BROWN, G. E., AND OTHERS. Toxic nephritis in pyloric and duodenal obstruction; renal insufficiency complicating gastric tetany. Arch. Int. Med. 32: 425-455, 1923

EDWARDS, J. G. The renal tubule (nephron) as affected by mercury. Am. J. Path. 18: 1011-1027, 1942

GOMORI, G. Calcification and phosphatase. Am. J. Path. 19. 197-209, 1943

GONZALES, T. A., VANCE, M., AND HELPERN, M.: Legal Medicine and Toxicology. New York, D. Appleton-Century, 1937.

HASKELL, C. C., CARDER, J. R., AND COFFINDAFFER, R. S. Value of forcing fluid in treatment of mercuric chloride poisoning. J. A. M. A. 81: 448-450, 1923

HEPLER, O. E., AND SIMONDS, J. P.: Experimental nephropathies III. Calcification and phosphatase in the kidneys of dogs poisoned with mercury

bichloride, potassium dichromate, and uranyl nitrate Arch Path 40: 37–43, 1945.

HUNTER, W C, AND ROBERTS, J M, Glomerular changes in the kidneys of rabbits and monkeys induced by uranium nitrate, mercuric chloride, and potassium bichromate Am J Path 8: 665–688, 1932

LAMBERT, S W, AND PATTERSON, H S Poisoning by mercuric chloride and its treatment Arch Int Med 16: 865–879, 1915

LONGCOPE, W T, AND LUETSCHER, J A, JR Clinical uses of 2,3 dimercaptopropanol (BAL) J Clin Invest 25: 557–567, 1946

——, AND —— The use of BAL (British anti-lewisite) in the treatment of injurious effects of arsenic, mercury and other metallic poisons Ann Int Med 31: 545–554, 1949

MACNIDER, W DE B Acute experimental nephritis Physiol Rev 4: 595–638, 1924

—— Urine formation during acute and chronic nephritis produced by uranium nitrate Harvey Lectures, 1928–9, p 82

MUNK, F Nierenkrankungen, 2nd ed Berlin, Wien, Urban and Schwarzenberg, 1925

PETERS, J P, EISENMANN, A J, AND KYDD, D M Mercury poisoning Am J M Sc 185: 149–171, 1933

PETRI, E Vergiftungen Handbuch der speziellen pathologischen Anatomie und Histologie, Henke, F and Lubarsch, O Vol X Berlin, J Springer, 1930

RICHARDS, A N Methods and Results of Direct Investigations of the Function of the Kidney Baltimore, Williams and Wilkins, 1929

ST GEORGE, A V Treatment of sepsis with Mercurochrome-220 soluble J A M A 85 2005–2008, 1925

SANSUM, W D Treatment in mercuric chloride poisoning J A M A 70: 824–828, 1918

WATERS, L L, AND STOCK, C B BAL (British anti-lewisite) Science 102: 601–606, 1945

WELLER, C V Calcification of the kidneys in bismuth poisoning Am J Path (Abst) 5: 541, 1929

WILMER, H A The mechanism of sucrose damage of the kidney tubules Am J Physiol 141: 431–438, 1944

ZEMAN, F D, FRIEDMAN, W, AND MANN, L T Kidney changes in pyloric obstruction Proc N Y Path Soc 24 41–46, 1924

*Poisons Bismuth, Lead and Bromate*

BLACKMAN, S S, JR Intranuclear inclusions in kidney and liver caused by lead poisoning Bull Johns Hopkins Hosp 58. 384–403, 1936

PAPPENHEIMER, A M, AND MAECHLING, E H Inclusions in renal epithelial cells following the use of certain bismuth preparations Am J Path 10. 577–588, 1934

WACHSTEIN, M Studies of inclusion bodies, acid fastness of inclusion bodies that are induced by ingestion of lead and bismuth Am J Clin Path 19. 608–614, 1949

WELLER, C V Calcification of the kidneys in bismuth poisoning Am J Path (Abst) 5: 541, 1929

*Glycols*

DUNN, J S, HAWORTH, A, AND JONES, N A Pathology of oxalate nephritis J Path & Bact 27: 299–318, 1924

GEILING, E M K, AND CANNON, P R Pathological effects of elixir sulfanilamide (diethylene glycol) poisoning, clinical and experimental correlation final report J A M A 111. 919–926, 1938

HUNT, R Toxicity of ethylene and propylene glycol Indust and Engin Chem 24: 361, 836, 1932

KESTEN, H D, MULINOS, M D, AND POMERANTZ, L Pathologic effects of certain glycols and related compounds Arch Path 27. 447–465, 1939

MILLES, G Ethylene glycol poisoning with suggestions for its treatment as oxalate poisoning Arch Path 41 631–638, 1946

PONS, C, AND CUSTER, R P Acute ethylene glycol poisoning, clinicopathologic report of 18 cases Am J M Sc 211: 544–552, 1946

*"Inclusion Disease"*

COWDRY, E V The problem of intranuclear inclusions in virus diseases Arch Path 18 527–542, 1934

FARBER, S, AND WOLBACH, S B Intranuclear and cytoplasmic inclusions ("protozoan like bodies") in salivary glands and other organs of infants Am J Path 8. 123–136, 1932

GOODPASTURE, E W Cellular inclusions and the etiology of virus diseases Arch Path 7. 114–132, 1929

——, AND TALBOT, F B Nature of "protozoan like" cells in certain lesions of infancy Am J Dis Child 21 415, 1921

JESIONEK AND KIOLEMENOGLOU Ueber einen Befund von protozoenartigen Gebilden in den Organen eines hereditarluetischen Fotus Munchen med Wehnschr 51 1905–1907, 1904

KINNEY, T D Intranuclear inclusions in infancy Am J Path 18: 799–811, 1942

LIPSCHÜTZ, B Untersuchungen uber die Aetiologie der Krankheiten der Herpesgruppe (Herpes zoster, Herpes genitalis, Herpes febrilis) Arch f Dermat u Syph 136: 428–482, 1921

OLITSKY, P K, AND HARFORD, C G Intranuclear inclusion bodies in the tissue reactions produced by injections of certain foreign substances Am J Path 13. 729–748, 1937

OPIE, E L The effect of injury by toxic agents upon osmotic pressure maintained by cells of liver and kidney J Exper Med 91: 285–294, 1950

PEARSON, E F Cytoplasmic inclusions produced by

the submaxillary virus Am J Path 6: 261-274, 1930

PINKERTON, H The morphology of viral inclusions and their practical importance in the diagnosis of human disease Am J Clin Path 20: 201-207, 1950

RIBBERT, H Ueber protozoenartige Zellen in der Niere eines syphilitischen Neugeborenen und in der Parotis von Kindern Centralbl f allg Path u path Anat 15. 945-948, 1904

SMITH, A J, AND WEIDMAN, F D Further note upon the occurrence of Endamoeba mortinatalium as a human parasite Am J Trop Dis 2: 256-259, 1914-15

TYZZER, E E The histology of the skin lesions in varicella J Med Res 14: 361-392, 1906

VELLIOS, F, AND SMITH, M G Fatal inclusion disease in newborn infants Am J Path (Sc Proc) 26. 667-668, 1950

VON GLAHN, W C, AND PAPPENHEIMER, A M Intranuclear inclusions in visceral disease Am J Path 1: 445-466, 1925

*Hemosiderosis*

DONATH, J, AND LANDSTEINER, K Über paroxysmale hämoglobinurie Munchen med Wchnschr 51: 1590-1593, 1904

GILLIGAN, D R, ALTSCHULE, M D, AND KATERSKY, E M Physiological intravascular hemolysis of exercise Hemoglobinemia and hemoglobinuria following cross country runs J Clin Invest 22: 859-869, 1943

——, AND BLUMGART, H L March hemoglobinuria, studies of the clinical characteristics, blood metabolism and mechanism, with observations on 3 new cases, and review of literature Medicine 20: 341-395, 1941

HADEN, R L Hemolytic anemia J Lab and Clin Med 26: 65-81, 1940

HASTINGS, A B, AND EISELE, C W Diurnal variations in acid base balance Proc Soc Exper Biol & Med 43: 308-312, 1940

HINMAN, F Principles and Practice of Urology Philadelphia, Saunders, 1935

JOSEPHS, H W Favism Bull Johns Hopkins Hosp 74: 295-298, 1944

KOSALKA, M F Multiple bee stings with hemoglobinuria and recovery, report of a case Bull U S Army Med Dept 9: 212-217, 1950

LUBRAN, M, AND SAKULA, J March hemoglobinuria Lancet 1: 435-438, 1949

LUISADA, A Favism, a singular disease chiefly affecting the red blood cells Medicine 20: 229-250, 1941

MCCRAE, T, AND ULLERY, J C Favism, report of a case J A M A. 101: 1389-1391, 1933

MANCHESTER, R C Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria Ann Int Med 23. 935-944, 1945

MARCHIAFAVA, E Anemia emolitica con emosiderosis perpetua Policlinico (sez med.) 35. 109-120, 1928, 38: 105-115, 1931

MICHELI, F Anemia (splenomegalia) emolitica con emoglobinuria-emosiderinuria tipo Marchiafava Haematologica, I. Arch 12: 101-123, 1931

OPIE, E L Cytochondria of normal cells, of tumor cells, and of cells with various injuries J Exper Med 86: 45-54, 1947.

ROBINSON, P Favism in children Am J Dis Child 62: 701-707, 1941

SCOTT, R B, ROBB SMITH, A H T, AND SCOWEN, E F The Marchiafava-Micheli syndrome of nocturnal hemoglobinuria with hemolytic anemia Quart J Med 7: 95-114, 1938

SUSSMAN, R M, AND KAYDEN, H J. Renal insufficiency due to paroxysmal cold hemoglobinuria Arch Int Med 82: 598-610, 1948

WHARTON, H J, AND DUESSELMANN, W. Favism, a short review and report of a case New England J Med 236: 974-977, 1947

*Hemoglobinuric Nephrosis*

ADDIS, T, MACKAY, E M, AND MACKAY, L L: Effect on kidney of long continued administration of diets containing excess of certain food elements J Biol Chem 71: 157-166, 1926

ALLEN, A C, AND SPITZ, SOPHIE A comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases Am J Path 21: 603-681, 1945.

ANDERSON, W A D, MORRISON, D B, AND WILLIAMS, E F, JR Pathologic changes following injections of ferrihemate (hematin) in dogs Arch Path 33: 589-602, 1942

ASSMANN, H, BIELENSTEIN, H, HABS, H., AND ZU JEDDELOH, B Beobachtungen und Untersuchungen bei der Haffkrankheit Deutsche med Wchnschr 59: 122-126, 1933

AYER, G D, AND GAULD, A. G Uremia following blood transfusion, nature and significance of renal changes Arch Path 33: 513-532, 1942

BIETER, R N The effects of the splanchnics upon glomerular blood flow in the frog's kidney Am J Physiol 91: 436-456, 1930

BING, R J The effect of hemoglobin and related pigments on renal functions of the normal and acidotic dog Bull Johns Hopkins Hosp 74: 161-176, 1944

BORDLEY, J, III Reactions following transfusion of blood with urinary suppression and uremia Arch Int Med 47: 288-315, 1931

BROWN, G E, ENSTERMAN, G B, HARTMAN, H R, AND ROWNTREE, L G. Toxic nephritis in pyloric and duodenal obstruction Renal insufficiency complicating gastric tetany Arch Int Med 32: 425-455, 1923

BURNETT, C H, SHAPIRO, S L, SIMEONE, F A, BEECHER, H K, MALLORY, T B, AND SULLIVAN, E. R. Renal function studies in the wounded Surgery 22: 856-873, 1947

BYWATERS, E G L, AND DIBLE, J H Renal lesion in traumatic anuria J Path & Bact 54: 111-120, 1942

CORCORAN, A C, AND PAGE, I H Crush syndrome, post-traumatic anuria Observations on genesis and treatment J A M A 134: 436-441, 1947

CREEVY, C D The importance of hemolysis during transurethral prostatic resection, a clinical investigation J Urol 59: 1217-1232, 1948

CUTHBERTSON, E M, AND GREENBERG, D M Chemical and pathological changes in dietary chloride deficiency in rat J Biol Chem 160 83-94, 1945

DUNN, J S, GILLESPIE, M, AND NIVEN, J S F Renal changes in 2 cases of crush syndrome Lancet 2. 549-552, 1941

DUNN, R C, AND WEBSTER, S H Hemoglobin crystals, casts, and globules in the renal tubules of guinea pigs following chemical hemolysis Am J Path 23 967-981, 1947

EAGLE, H Recent advances in blood coagulation problem Medicine, 16 95-138, 1937

FAIRLEY, N H Fate of extracorpuscular circulating hemoglobin Brit M J 2. 213-217, 1940

FRENCH, A J Glomerulonephrosis a morphologic manifestation of renal cortical ischemia in toxic oliguria and lower nephron nephrosis Arch Path 49: 43-54, 1950

FRIES, W P Sulfathiazole anuria cured by means of intravenous procaine treatment J Urol 61: 184-186, 1949

GILLIGAN, D R, ALTSCHULE, M D, AND KATERSKY, E M Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions J Clin Invest 20: 177-187, 1941

——, AND BLUMGART, H L March hemoglobinuria, studies of clinical characteristics, blood metabolism and mechanism, with observations on 3 new cases and review of literature Medicine 20 341-395, 1941

GOODPASTOR, W E, AND OTHERS Clinical and pathologic study of kidney in patients with thermal burns Surg, Gynec, & Obst 82. 652-670, 1946

GOORMAGHTIGH, N Vascular and circulatory changes in renal cortex in anuric crush syndrome Proc Soc Exper Biol & Med 59 303-305, 1945

KIMMELSTIEL, P Acute hematogenous interstitial nephritis Am J Path 14 737-761, 1938

KIRSNER, J B, AND KNOWLTON, K Acid base balance, renal function, and gastric secretion during hypochloremia in the dog J Clin Invest 20. 303-312, 1941

LANDSTEINER, E K, AND FINCH, C A Hemoglobinemia accompanying transurethral resection of the prostate New England J Med 237: 310-312, 1947

LANGERON, L, PAGET, M, AND MICHAUX, P Anurie par le sulfathiazol Anurie sécrétoire Blocage tissulaire Action remarquable de la scurocaine intraveineuse Bull et mém Soc méd d hôp de Paris 62: 58-61, 1946

LAUSON, H D, BRADLEY, S E, AND COURNAND, S E Renal circulation and shock J Clin Invest 23. 381-402, 1944

LUCKÉ, B Lower nephron nephrosis (renal lesions of crush syndrome, of burns, of transfusions, and other conditions affecting lower segment of nephrons) Mil Surgeon 99: 371-396, 1946

McLETCHIE, N G B Renal lesions in case of excessive vomiting J Path & Bact 55: 17-22, 1943

McMANUS, J F A Medical Diseases of the Kidney (An Atlas and Introduction) Philadelphia, Lea and Febiger, 1950

MAEGRAITH, B G, AND FINDLAY, G M Oliguria in blackwater fever Lancet 2. 403-404, 1944

MALLORY, T B Hemoglobinuric nephrosis in traumatic shock Am J Clin Path 17: 427-443, 1947

MARSHALL, D, AND HOFFMAN, W S The nature of the altered renal function in lower nephron nephrosis J Lab & Clin Med 34: 31-39, 1949

MARTINEAU, P C, AND HARTMAN, F W Renal lesions in extensive cutaneous burns J A M A 134 429-436, 1947

MILLIKAN, G A Muscle hemoglobin Physiol Rev 19. 503-523, 1939

MINAMI, S Über Nierenveranderungen nach Verschuttung Virchow's Arch f path Anat 245: 247-267, 1923

MOLONEY, W C, STOVALL, S L, AND SPRONG, D H, JR Renal damage due to ischemic muscle necrosis J A M A 131: 1419-1420, 1946

PETERS, J T Oliguria and anuria due to increased intrarenal pressure Ann Int Med 23: 221-236, 1945

RICHARDS, A N Direct observations of change in function of the renal tubule caused by certain poisons Tr A Am Physicians 44: 64-67, 1929

—— Methods and Results of Direct Investigations of the Function of the Kidney Baltimore, Williams and Wilkins, 1929

ROSS, J F Medical progress hemoglobinemia and hemoglobinurias New England J Med 233 691, 732, 766, 1945

SIROTA, J H Carbon tetrachloride poisoning in man I The mechanisms of renal failure and recovery J Clin Invest 28: 1412-1422, 1949

SMITH, H W Note on the interpretation of clearance methods in the diseased kidney J Clin Invest 20: 631-635, 1941

SPITZ, SOPHIE The pathology of acute falciparum malaria Mil Surgeon 99. 555-572, 1943

TRUETA, J, BARCLAY, A E, DANIEL, P M, FRANKLIN, K J, AND PRICHARD, M M L Studies of the Renal Circulation Springfield, Ill, C C Thomas, 1947

VANDER WEER, J B, AND FARLEY, D L Mushroom poisoning (mycetismus), report of 4 cases Arch Int Med 55 773-791, 1935

WIENER, A S, AND PETERS, H R Hemolytic reactions following transfusions of blood of homologous group, with a case in which same agglutinogen was responsible Ann Int Med 13: 2306–2322, 1940

——, AND SCHAEFER, G Limitations in use of preserved blood for transfusion, study of fate of transfused erythrocytes in recipient's circulation M Clin North America 24: 705–722, 1940

WOODRUFF, L M, AND FIRMINGER, H I Hemoglobinemia and hemoglobinuric nephrosis complicating transurethral resection of the prostate J Urol 62. 168–177, 1949

YOUNG, J Renal failure after uteroplacental damage Brit M J 2. 715–718, 1942

YUILE, C L Hemoglobinuria Physiol Rev 22: 19–31, 1942

——, GOLD, M A, AND HINDS, E G Hemoglobin precipitation in renal tubules, a study of its causes and effects J Exper Med 82: 361–374, 1945

——, STEINMAN, J B, HAHN, P F, AND CLARK, W F The tubular factor in renal hemoglobin excretion J Exper Med 74: 197–202, 1941

### *Cholemic Nephrosis*

BOYCE, F F The Role of the Liver in Surgery Springfield, Ill, C C Thomas, 1941

COMFORT, M W, BARGEN, J A, AND MORLOCK, C G The association of chronic ulcerative colitis (colitis gravis) with hepatic insufficiency, report of four cases M Clin North America 22: 1089–1097, 1938

COUNCILMAN, W T Description of the pathological histology of yellow fever In Report on the Etiology and Prevention of Yellow Fever by G Sternberg Pub Health Bull 2: 151–153, 1890

COX, G J, SMYTHE, C V, AND FISHBACK, C F The nephropathic action of cystine J Biol Chem 82. 95–103, 1929

GARLOCK, J H, AND KLEIN, S H The so-called hepato renal syndrome Ann Surg 107: 82–95, 1938

HELWIG, F C, AND ORR, T G Traumatic necrosis of liver with extensive retention of creatinine and high grade nephrosis Arch Surg 24: 136–144, 1932

——, AND SCHUTZ, C B A liver kidney syndrome Clinical, pathological, and experimental studies Surg, Obst, & Gynec, 55. 570–580, 1932

HEYD, C G Concept of liver deaths J A M A 121: 736–737, 1943

JONES, G W, BAGGENSTOSS, A H, AND BARGEN, J A The liver in chronic ulcerative colitis Proc Staff Meet Mayo Clinic 25. 251–256, 1950

KUZMA, J L AND POLLEY, T Z The role of the liver in renal sulfonamide complications Am J M Sc 214: 651–665, 1947

LILLIE, R D Histopathologic changes produced in rats by the addition to the diet of various amino acids Pub Health Rep 47: 83–93, 1932

MOREHEAD, R P, FISHMAN, W H, AND ARTOM, C · Renal injury in the rat following the administration of serine by stomach tube Am J Path 21: 803–815, 1945

NEWBURGH, L H, AND MARSH, P. L Renal injuries by amino acids Arch. Int Med. 36: 682–711, 1925

SMETANA, H Nephrosis due to carbon tetrachloride Arch Int Med 63: 760–777, 1939

SUTTON, J E · Acute postoperative necrosis of the liver (So-called high-temperature liver death syndrome) Am J M Sc 192: 219–224, 1936

WILENSKY, A O Occurrence, distribution and pathogenesis of so called liver death and/or hepatorenal syndrome Arch Surg 38: 625–691, 1939

### *Sulfonamide Nephrosis*

ABESHOUSE, B S, AND TANKIN, L H Renal complications of sulfonamide therapy J Urol 56: 658–687, 1946

ALLEN, A C Medical Diseases of the Kidney Army Inst of Path Registry Press 1947

ANTOPOL, W, AND ROBINSON, H. J. Pathologic and histologic changes following oral administration of sulfapyridine with short note on sodium sulfapyridine Arch Path 29: 67–76, 1940

CLIMENKO, D R., AND WRIGHT, A W Effects of continued administration of sulfathiazole and sulfapyridine in monkeys Arch Path 32: 794–817, 1941

DUFF, G L, AND MURRAY, E G D Pathologic lesions following the administration of sulfonamide drugs Am J M Sc 205: 439–454, 1943

FRENCH, A J Hypersensitivity in pathogenesis of histopathologic changes associated with sulfonamide chemotherapy Am J Path 22: 679–701, 1946

GROSS, P, COOPER, F B, AND SCOTT, R E Urolithiasis medicamentosa Urol & Cutan Rev 44. 205–209, 1940

——, ——, AND LEWIS, M Urinary concretions caused by sulfapyridine Proc Soc Exper Biol & Med 40: 448–449, 1939

KATZENSTEIN, R, AND WINTERNITZ, M C Necrosis of renal pelvis associated with obstruction of ureters Yale J Biol & Med 14: 257–267, 1942

KOLETSKY, S, AND KING, B G Fatal renal insufficiency following administration of sulfapyridine J Lab & Clin Med 25 1021–1025, 1940

KUZMA, J F, AND POLLEY, T Z The role of the liver in renal sulfonamide complications Am J M Sc 214: 651–655, 1947.

LEDERER, M, AND ROSENBLATT, P Death during sulfathiazole therapy; pathologic and clinical observations on 4 cases with autopsies J A M A 119: 8–18, 1942

LEHR, D Inhibition of drug precipitation in the urinary tract by the use of sulfonamide mixtures

I Sulfathiazole-sulfadiazine mixture Proc Soc Exper Biol & Med 58, 11-14, 1945
MORE, R H, MCMILLAN, G C, AND DUFF, G L The pathology of sulfonamide allergy in man Am J Path. 22: 703-735, 1946
MURPHY, F. D, KUZMA, J F, POLLEY, T Z, AND GRILL, J Clinicopathologic studies of renal damage due to sulfonamide compounds, report of 14 cases Arch Int Med 73 433-443, 1944
PRIEN, E L Mechanism of renal complications in sulfonamide therapy New England J Med 232, 63-68, 1945
RICH, A R The role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy Bull Johns Hopkins Hosp 71: 123-140, 1942
SADUSK, J F, WATERS, L L, AND WILSON, D Treatment of anuria due to sulfapyridine calculi J A M A 115: 1968-1973, 1940
SCHIFRIN, A, AND KELSON, S A case of massive urolithiasis following massive doses of heparin and sulfapyridine for subacute bacterial endocarditis due to infection with Streptococcus viridans Arch Path 30: 983-984, 1940
SOBIN, S S, ARONBERG, L M, AND ROLNICK, H C Nature of renal lesion with sulfonamides and its prevention with urea Am J Path 19: 211-233, 1943
STRYKER, W A Nature of renal lesion with sulfapyridine therapy J A M A 114: 933-954, 1940
VAN DYKE, H B, GRUP, R O, RAKE, G, AND MCKEE, C M Observations on toxicology of sulfathiazole and sulfapyridine Proc Soc Exper Biol & Med 42: 410-416, 1939

*Von Gierke's Disease*

ANTOPOL, W, HEILBRUNN, J, AND TUCHMAN, L Enlargement of the heart due to abnormal glycogen storage in von Gierke's Disease Am J M Sc 188. 354-359, 1934
VON GIERKE, E Hepato nephromegalia glykogenica (Glycogenspeicherkrankheit der Leber und Nieren) Beitr z path Anat u z allg Path 82. 497-513, 1929.
HUMPHREYS, E Glycogen storage disease Thesaurismosis glycogenica (von Gierke) Am J Path 10 589-614, 1934
KIMMELSTEIL, P Über Glykogenose Beitr z path Anat u z allg Path 91. 1-18, 1933
MASON, H H, AND ANDERSON, D H Glycogen disease Am J Dis Child 61. 795-825, 1941
POPPER, H, AND WOZASEK, O Zur Kenntnis des Glycogengehaltes der Leichenleber Virchow's Arch f path Anat 279 819-868, 1931
PUTSCHAR, W Über angeborene glycogenspeicher-Krankheit der Herzens—"Thesaurismosis glycogenica" (v Gierke) Beitr z path Anat u z allg Path 90. 222-232, 1932
SCHOENHEIMER, R Über einer eigenartige Storung des Kohlehydrat-stoffwechsels Ztschr f physiol Chem 182: 148-150, 1929
WACHSTEIN, M Glycogen storage (von Gierke's) disease predominantly involving the heart Report of a case with histochemical phosphatase studies Am J M Sc 214: 401-409, 1947

*Myeloma Nephrosis*

ADAMS, W S, ALLING, E L, AND LAWRENCE, J S Multiple myeloma Its clinical and laboratory diagnosis with special emphasis on electrophoretic abnormalities Am J Med 6. 141-161, 1949
APITZ, K Allgemeine Pathologie der menschlichen Leukämien Ergebn d allg Path u path Anat 35. 1-104, 1940
ARMSTRONG, J B A study of renal function in patients with multiple myeloma Am J M Sc 219. 488-493, 1950
BANNICK, E K, AND GREENE, C H Renal insufficiency associated with Bence-Jones proteinuria, report of 13 cases with note on changes in serum proteins Arch Int Med 44 486-510, 1929
BELL, E T Renal lesions associated with multiple myeloma Am J Path 9 393-420, 1933
BEWLEY, G Bence-Jones proteinuria Irish J M Sc 6 321-325, 1927
BOGGS, T R AND GUTHRIE, C G The Bence-Jones proteinuria in conditions other than myelomatosis, an instance associated with metastatic carcinoma Bull Johns Hopkins Hosp 23: 353-356, 1912
VON DECASTELLO, A Beitrage zur Kenntnis der Bence-Jonesschen Albuminurie Ztschr f klin Med 67. 319-343, 1908-9
FOORD, A G Hyperproteinemia, autohemagglutination, renal insufficiency and abnormal bleeding in multiple myeloma Ann Int Med 8: 1071-1089, 1935
FORBUS, W D, PERLZWEIG, W A, PARFENTJEV, I A, JR Bence Jones protein excretion and its effect upon the kidney Bull Johns Hopkins Hosp 57. 47-69, 1935
GLAUS, A Ueber multiples Myelozytom mit eigenartigen, zum Teil kristallahnlichen Zellein lagerungen, kombiniert mit Elastolyse und ausgedehnter Amyloidose und Verkalkung Virchow's Arch f path Anat 223. 301-339, 1917
HEWITT, L F Bence-Jones proteins Biochem J 23 1147-1152, 1929
HOLMAN, R L Complete anuria due to blockage of renal tubules by protein casts in a case of multiple myeloma Arch Path 27: 748-752, 1939
JACOBSON, B M, AND WILNER, L R The detection of urinary Bence-Jones protein Am J Clin. Path 14 138-149, 1944
LOHLEIN, M Eiweisskristalle in den Harnkanälchen bei multiplem Myelom Beitr z path Anat u z allg Path 69 295-304, 1921

MacMahon, H E, and Magnus-Levy, A Renal lesions in experimental Bence-Jones proteinuria Abst Am J Path 12: 763–766, 1936

Miller, S R, and Baetjer, W A Bence-Jones proteinuria, some observations on its occurrence with particular reference to nephritis and hypertension J A M A 70: 137–139, 1918

Neumann, V Multiple plasma-cell myeloma with crystalline deposits in the tumour cells and in the kidneys J Path & Bact 61: 165–169, 1950

Perla, D, and Hutner, L: Nephrosis in multiple myeloma Am J. Path. 6: 285–298, 1930

Sikl, H · A case of diffuse plasmacytosis with deposition of protein crystals in the kidneys J. Path & Bact. 61: 149–163, 1950.

*Gout*

Brown, J, and Mallory, G K. Renal changes in gout New England J Med 243: 325–329, 1950

Schnitker, M A., and Richter, A. B Nephritis in gout. Am. J. M. Sc. 192: 241–252, 1936

# 8. Interstitial Nephritis

## Acute Diffuse Interstitial Nephritis

### *Introduction*

Acute diffuse interstitial nephritis complicates bacterial, rickettsial, and viral infections, as well as the administration of sulfonamides, and possibly other chemicals More specifically, this form of nephritis has followed diphtheria, scarlet fever, Ludwig's angina, erysipelas, typhoid fever, infected wounds, typhus fevers, smallpox, measles, and other diseases The clinical manifestations are likely to occur earlier in the course of the disease, often during the first week, for example, than does the acute diffuse glomerulonephritis after scarlet fever Acute diffuse interstitial nephritis is rarely diagnosed clinically although it would seem that the early onset of moderate to severe oliguria, or, rarely, anuria, with azotemia without other apparent cause, might lead to the suspicion of acute interstitial nephritis, especially in infectious diseases Hypertension and edema are not present, albuminuria is slight or absent, hematuria and slight pyuria occur occasionally

### *Pathology*

#### *Gross appearance*

The kidneys are soft and enlarged from one and a half to twice normal size The capsules are easily stripped from a smooth, mottled, purple-red, yellowish-brown, often finely hemorrhagic surface The sectioned surface is moist, and is characterized by a thickened cortex, discolored with linear streaks of cellular infiltrate in contrast to the deep red of the adjacent hyperemic vessels The medulla is deeply congested

#### *Histologic appearance*

The histologic picture of acute interstitial nephritis varies in the quality of the cells constituting the infiltrate In all cases, however, it would seem best to adopt the requirement that the diagnosis of acute interstitial nephritis be based on the actual finding of infiltrate *diffusely* throughout the kidney, and, above all, within the cortical interstitium

The infiltrate is composed predominantly either of plasma cells, or of eosinophilic leukocytes (plates 156 A, 157) In some instances, the infiltrate is made up of a mixture of plasma cells, eosinophilic leukocytes, and scattered polymorphonuclear leukocytes and histiocytes Occasionally the inflammatory cells undergo karyorrhexis The amount of interstitial edema is variable, a separate designation of "serous" interstitial nephritis does not appear justified Focal hemorrhages may be present There is no distinction between the infiltrate provoked by products of bacteria and that produced by the sulfonamides.

The glomeruli are not histologically altered The tubules appear intact except for frequent foci of hyaline granular degeneration of the epithelium of the proximal convoluted tubules Small clusters of purulent exudate are scattered in the distal tubules, even when the interstitial infiltrate is almost exclusively plasmocellular (plate 157 C) The vessels generally are not remarkable although, occasionally, focal thrombophlebitis and an acute fibrinoid smudgy degeneration of an isolated arteriole may be noted The peritubular capillaries are often filled with mononuclear cells that are not representative of the peripheral blood and appear to be the source of the interstitial infiltrate (plate 170 A).

Undoubtedly less severe degrees of acute diffuse interstitial nephritis remain undiagnosed and are survived It is likely that restitution in such cases takes place, not by scarring but by complete resolution The terms chronic interstitial nephritis or chronic parenchymatous nephritis have become obsolete and should not be regarded as the chronic stage of acute interstitial nephritis

The acute diffuse interstitial nephritis is probably invariably fatal. It still remains unclear precisely how the renal shutdown is produced by the interstitial infiltrate. The ob-




FIG A *Acute interstitial nephritis* following scarlet fever The infiltrate consists chiefly of lymphocytes and plasma cells with a scattering of polymorphonuclear leukocytes The tubules are preserved although some contain exudate

FIG B *Lymphosarcoma* of kidney in which interstitial neoplastic cells superficially simulate acute interstitial nephritis

FIG C *Leukemia* of kidney which, in this interstitial form, also simulates acute interstitial nephritis

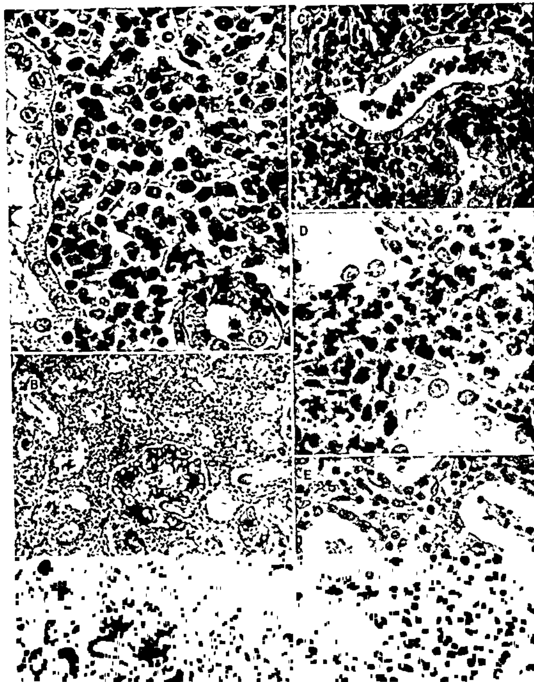



Fig A [illegible]

many plasma cells and lymphocytes

Fig B *Acute interstitial nephritis superimposed on amyloidosis* of the kidney

Fig C. *Exudate in distal convoluted tubule in acute interstitial nephritis*

Fig D *Necrobiotic distortion* of polynuclear cells in interstitium in acute interstitial nephritis

Fig E *Interstitial edema* in acute interstitial nephritis

vious presumption is that the infiltrate increases intrarenal pressure with compression of vessels The pressure is apparently not relieved by decapsulation Moreover, an even more compact and extensive interstitial infiltrate occurs relatively frequently in the various lymphoblastomas and leukemias without renal dysfunction (plate 319 C). Possibly the difference is dependent on the rapidity with which the infiltrate is deposited

### *Pathogenesis*

Fishberg's suggestion that "acute interstitial nephritis is due to invasion of the kidneys by organisms rather than to the action of the toxic products as in glomerulonephritis" is not the most credible interpretation of the pathogenesis of this disease Positive cultures of the kidneys in the presence particularly of sepsis but also of postmortem invasion of bacteria must obviously be given little weight. The finding of culpable bacteria within inflammatory foci of paraffin sections of kidneys with acute diffuse interstitial nephritis is extremely uncommon and would certainly not seem to merit *direct* causal association The more plausible concept is that the diffuse interstitial inflammation is the reaction either to toxic products of bacteria, rickettsias, or viruses, or their allergens

In view of the occurrence of acute interstitial nephritis as a reaction to sulfonamides, the role of allergens with various haptenes is stressed To dismiss the possibility of allergy or altered local tissue reactivity in the pathogenesis of a lesion in humans because of the time relationship to the initial infection is unwarranted Furthermore, to suggest that when the glomeruli are involved in an acute glomerulonephritis, the pathogenesis must be different from that concerned with inflammation of the interstitium merely because the two structures are so completely different, is to overlook a basic feature of the target of allergens In other words, some patients with allergy will react with asthma, others with similar allergies will develop a skin rash, and still others will manifest their allergy with an acute peritoneal reaction, or intestinal upset. Similarly, glomeruli may be the target in one case, the interstitium in another, the vessels in the third. Moreover, it is becoming increasingly clear that neither eosinophilic leukocytic inflammation, nor fibrinoid degeneration constitute the only response to allergy Plasma cells, various histiocytes, and lymphocytes (Allen and Spitz) are also concerned, often to the exclusion of eosinophilic leukocytes.

### Acute Focal Interstitial Nephritis

The acute focal interstitial nephritis is to be distinguished histologically from acute diffuse interstitial nephritis. The failure to establish this distinction has been responsible for some confusion in the literature. Acute *focal* interstitial nephritis may occur in association with any sepsis, including Weil's disease (plate 106 A), as a reaction to a variety of drugs and poisons, and in hemoglobinuric and cholemic nephrosis, and possibly in syphilis. This focal interstitial reaction in the kidney may be indistinguishable from that of infectious mononucleosis. Rarely is the focal infiltration so extensive as to be solely responsible for the degree of renal insufficiency that occurs in the diffuse disease In the focal disease, the infiltrate tends to localize at the corticomedullary junction or even exclusively in the medulla (plate 171 A).

### References

Allen, A C Medical Diseases of the Kidney Army Inst of Path Registry Press 1947

——, and Spitz, S A comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases Am J Path **21**: 603–681, 1945

Councilman, W T. Acute interstitial nephritis J Exper Med **3**: 393–420, 1898

Fishberg, A M Hypertension and Nephritis Philadelpia, Lea and Febiger, 1939.

Matthews, W R · Acute hematogenous interstitial nephritis South M J. *36*: 1055–1063, 1942

# 9. Specific Infections

## Tuberculosis

### *Introduction*

Perhaps one of the most satisfactory viewpoints of the pathogenesis of organ tuberculosis is embodied in Ranke's classification of tuberculosis (Jaffé). According to this classification, four stages in the evolution of tuberculous infection occur:

1. The stage of the primary complex
2. The stage of early generalization
3. The stage of localization
4. The stage of late generalization

The primary (Ghon) complex (parenchymal infection plus the lymph node component) occurs principally in the lung, but may occur at a variety of other sites including the intestine or even the penis after circumcision. The establishment of the primary complex, which tends to become calcified, is followed in the next few years by the stage of early generalization. This stage takes place usually in childhood and is generally overlooked clinically because of the mildness of the symptoms. As a result of this early dissemination, the tubercle bacilli may persist in a dormant state for years in one or more organs. A healed lesion of this sort is illustrated in plate 162 B. These organisms are activated in later life when "resistance" is lowered for one of a variety of reasons (for example, undernourishment, debilitating diseases, or diabetes mellitus). Fatal miliary dissemination or the final stage of "late generalization" may then result from the isolated organ tuberculosis thus produced.

There has been criticism of this concept of tuberculosis as there has been of most. An alternate concept is that the tubercle bacilli do not lie latent in the kidney—or other organ in question—but reach it by the hematogenous seeding of organisms from an activated focus usually in the form of an apical or subapical (Aschoff-Puhl or Simon) lesion. In either instance the renal localization is from a hematogenous dissemination of bacilli. The renal localization through lymphatic spread or by direct ascension from the lower urogenital tract probably accounts for a very small fraction of cases of renal tuberculosis unlike the suppurative pyelonephritis secondary to cystitis and ureteritis caused by pyogenic organisms.

### *Miliary Renal Tuberculosis*

Miliary renal tuberculosis follows a hematogenous dissemination of tubercle bacilli (Ranke, stage IV) from an activated focus in the kidney itself or some other organ. Renal miliary tuberculosis is therefore a part of a generalized miliary tuberculosis; obversely, in most cases of death due to miliary tuberculosis, the kidneys are involved. This overwhelming form of tuberculosis is rarely recognized clinically because it occurs so soon before death and does not lead to significant renal dysfunction. The latent dissemination of early tuberculosis (Ranke, stage II) may lead to a few miliary renal tubercles which subsequently heal completely or, as stated, act as a latent focus for future activation (plate 162 B).

The miliary tubercles, unlike the lesions of clinical renal tuberculosis, are localized largely to the cortex, however, they may also involve the medulla (plate 160 B). Rarely, a histologic picture superficially resembling focal endocarditic glomerulonephritis is noted.

### *Ulcero-caseous Renal Tuberculosis*

The lesions that result in chronic destructive renal tuberculosis select the pyramid—usually at its apex rather than its base—for the site of initial localization (plate 160 A). It is interesting that the organs such as the liver and spleen which are heavily seeded with tubercles in miliary tuberculosis are rarely involved by extensive ulcero-caseous tuberculosis, in contrast to the kidneys (Rich). The mere contact of tissues with numbers of bacilli is

not the answer to this disparity The involvement is usually unilateral for a while but, sooner or later, the opposite organ is affected The explanation of the tendency for bilateral involvement of paired organs is also incomplete For example, if the left kidney is tuberculous, why does not the left adrenal become involved before the right kidney Common connecting channels can not be the entire explanation in view of the situation applying to the adrenals as well (Rich)

The tuberculous focus of the pyramids tends to begin at either pole of one kidney and to spread by ulceration and cavitation outward to the entire pyramid and cortex and inward to involve the pelvic mucosa The caseation may simulate grossly the lesions of necrotizing papillitis (plate 161 C) With ulceration through the papilla, the process spreads to other papillae, to the mucosa of the entire pelvis and to the ureter The progressive caseous destruction and cavitation may lead to a bosselated enlargement of the kidney to 1½ to 2 times the normal size. The sectioned surface of such an organ with tuberculous pyonephrosis shows it to be hydronephrotic with cavities lined by ragged granular cavities with caseous yellow walls in place of the pyramids, yellowish grey streaks and nodules in the adjacent cortex, and ulceration and thickening of the pelvis (plate 161 A).

The stage of the lesion may vary from one part of the kidney to another. Irregular areas of fibrosis and calcification may occur The perirenal fat and capsule may become markedly scarred and adherent to the kidney and other structures The pelvic infection may extend to the ureter causing ulcerative thickening of its wall and stricture of its lumen with consequent aggravation of the hydronephrosis There appears to be no positive correlation between the extent of the involvement of the kidney on the one hand, and the ureter on the other Actually the lesion referred to as the "closed" or "putty" kidney is one characterized by complete pultaceous destruction of the kidney without ureteral involvement This process is sometimes called "autonephrectomy" and occurs in about 10 per cent of cases of tuberculous pyonephrosis and, with an adequate opposite kidney, may be survived by the patient for many years.

Renal tuberculosis is often masked clinically because the symptoms are often interpreted as primarily due to the bladder. Frequency of urination, both day and night, dull local pain, dysuria, dribbling, microscopic hematuria (gross hematuria is rare) and "sterile" pyuria (with ordinary stains) are the common symptoms There may be a remarkable lack of constitutional symptoms despite apparently extensive renal involvement.

*Toxic Tuberculous Nephritis*

"Toxic nephritis" caused by tuberculosis is mentioned in text books as one of the varieties of renal tuberculosis Apart from the gamut of changes that may occur within a tubercle, we have no personal information as to precisely what this term means, nor is it defined histologically in the texts It is well known that diffuse glomerulonephritis is a rare complication of pulmonary tuberculosis (15 cases in 2800 patients, Holten) and even when it does occur in such cases, secondary invaders might have been the responsible agents

RENAL SARCOIDOSIS

Sarcoidosis of the kidney is a rare histologic finding Sarcoidosis has been reported as being responsible for renal insufficiency (Klinefelter and Salley), but histologic documentation is lacking In those cases that were examined pathologically, only infrequent and isolated foci of sarcoidosis were found as in the case illustrated in plate 163 Spencer and Warren in 1938 stated that theirs was the first report of renal sarcoidosis Longcope in 1941 observed the renal lesions in 3 of 4 autopsied cases of sarcoidosis The sarcoid tubercles in the kidney are quite like those in other organs, consisting of "hard," epithelioid, noncaseating tubercles with giant cells and even Schaumann bodies (plate 163 B) No asteroid bodies were found in the few tubercles seen in our case, nor are they mentioned in the reports of others on the renal lesions Renal calculi may be associated

with generalized sarcoidosis (Albright and Reifenstein).

### Syphilitic Lesions of the Kidney

The following lesions of the kidney have been attributed to syphilis.

1. Congenital interstitial nephritis
2. Gumma
3. "Nephrosis"
4. Focal interstitial nephritis (Rich)
5. Hemosiderosis and hemoglobinuric nephrosis (rarely) secondary to paroxysmal cold hemoglobinuria

1 *Congenital interstitial nephritis*

The kidney of congenital syphilis is characterized by interstitial inflammation in association with great numbers of treponemas in the interstitium, in the tubular lumens, and among the tubular epithelial cells.

2 *Gumma*

The syphilitic gumma of the kidney is now rarely seen The histologic picture is that of a gumma in other organs Some observers have regarded multiple irregular scars in the kidneys of syphilitic individuals as healed gummas, principally on the basis of exclusion of other diseases For all practical purposes, the renal gumma is an obsolete lesion

3 *Syphilitic "nephrosis"*

There is said to be a third form of renal involvement in syphilis which is manifested clinically by the sudden onset of the nephrotic syndrome without renal insufficiency, usually in the secondary stage, and which is stated to clear promptly with antiluetic therapy (Heyman and Brown) Some cases, nonetheless, do not respond to antiluetic or any other type of therapy (Fishberg). The histologic proof of the existence of such a specific lesion is not complete However, the dramatic clinical response to antiluetic treatment makes it highly probable that syphilis is etiologically concerned. Until adequate histologic evidence is presented, it might be provisionally assumed that there develops a remarkably acute, increased glomerular permeability, probably of the order of membranous glomerulonephritis As a matter of fact, doubly refractive lipid bodies may be found in the urine (Munk) This type of lesion is not characterized by distortion of the architecture so that it conceivably could be quickly restored The resistance of other forms of membranous glomerulonephritis to therapy is difficult to understand in the light of the response of the luetic nephrosis The syphilitic nephrosis responds poorly to mercurial antiluetic therapy, well to arsenical therapy, and best to penicillin therapy (Barr et al )

4. *Syphilitic focal interstitial nephritis*

About a decade ago, a distinctive type of nonsymptomatic syphilitic damage to the kidneys of patients with secondary syphilis was described by Rich. Grossly, these kidneys showed glistening, greyish yellow flecks beneath the capsule and deeper in the cortex. These foci project from the cut surface very much as shining grains of sand In later stages, these flecks may be associated with small irregular scars Microscopically, the lesions are characterized by spherical nodules of interstitial inflammatory cells which invaginate the wall of a tubule into its lumen (plate 164). These inflammatory herniating knobs represent the constant feature of the lesion The infiltrate consists of histiocytes, lymphocytes and rare plasma cells along with a few eosinophilic leukocytes

The second prominent feature of the process is the presence in the tubular lumens of cholesterol crystals in the midst of lipoid macrophages, other mononuclear cells, polymorphonuclear leukocytes, and cellular debris Such foci may be rare or numerous but not so frequent as to interfere with renal function The glomeruli are not altered unless they happen to be caught within the inflammatory areas wherein they, as well as the adjacent tubules, may become atrophic There may be considerable perivascular infiltration of mononuclear cells but no significant intrinsic vascular alteration indicative of syphilis It appears probable that a more advanced phase of the process is characterized by focal irregular scars Unlike con-

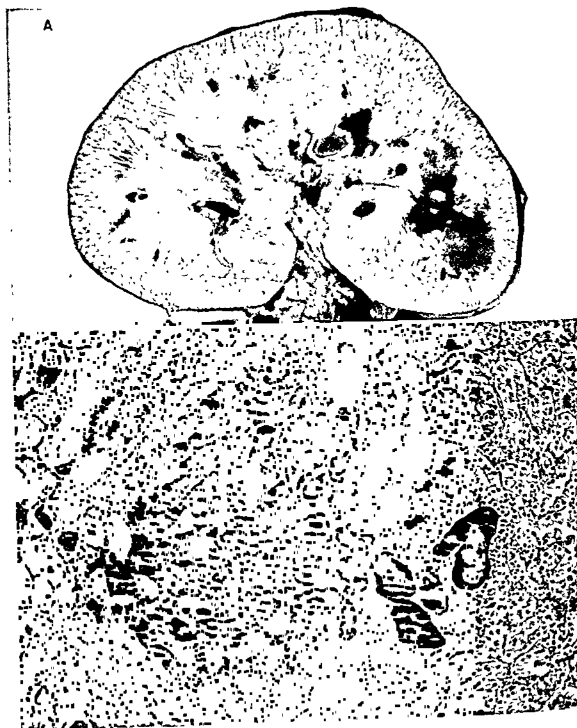



FIG A *Kidney of bubonic plague* shows pallor and swelling.

FIG B *Renal abscess* in bubonic plague Numerous plague bacilli are present in the tubular casts

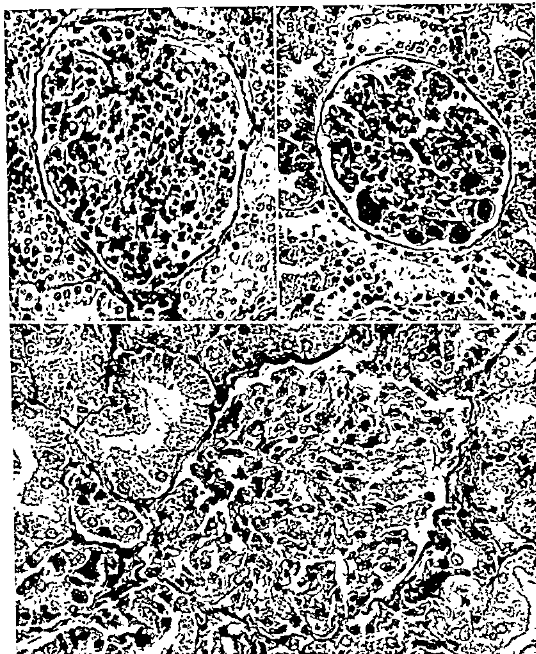


FIG. A *Acute diffuse proliferative glomerulonephritis* in bubonic plague

FIG B. *Thrombi in glomerular capillaries* due to dehydration and shock in bubonic plague

FIG C *Glomerulonephritis in cholera* Note the swollen thickened basement membranes of the ischemic glomerulus and the epithelial vacuolization of the proximal tubules (osmotic nephrosis) Another coarser type of vacuolization may also be observed (see plates 107 and 108)













FIG A *Tuberculous pyelonephritis*

FIG B. *Miliary tuberculosis* of kidney.

FIGS C AND D *Miliary tubercles* in kidney.




FIG A *Hydronephrotic atrophy* in caseous renal tuberculosis

FIG B *Caseous tuberculosis* of kidney selectively destroying the pyramids

FIG C *Necrotizing papillitis* simulating tuberculosis

genital luetic nephritis which shows an abundance of spirochetes, as yet, spirochetes have not been demonstrated in these lesions, nor, it appears, in any other *acquired* luetic lesion of the kidney Recently we have seen three instances of this lesion in the kidneys of *nonsyphilitic* white patients with varying degrees of pyelonephritis (plate 164) These latter lesions are indistinguishable from those described by Rich as specific Nevertheless, this type of focal interstitial nephritis *does* appear to occur with a significantly higher incidence in syphilitic than nonsyphilitic patients. The possibility of the occurrence of a focal interstitial nephritis (and of perhaps other acute forms of lesions) as a result of a Herxheimer reaction cannot be excluded.

*Hemosiderosis and hemoglobinuric nephrosis*

Paroxysmal cold hemoglobinuria is a rare disorder which occurs chiefly in individuals with syphilis, generally of the congenital type. Its effect on the kidney is almost always inconsequential, consisting of hemosiderosis of the proximal tubules, as in Marchiafava-Micheli's disease. An instance of fatal hemoglobinuric nephrosis at least *associated* with paroxysmal cold hemoglobinuria has recently been reported (Sussman and Kayden) However, this case had complicating features so that hemoglobinuric nephrosis should not be considered an intrinsic part of paroxysmal cold hemoglobinuria.

## Relapsing Fever

Relapsing fever is a louse- and tick-borne acute febrile disease caused by the diverse strains of borrelia, of which the most important are *B recurrentis* (louse-borne) and *B duttoni* (tick-borne). The organisms were originally regarded as treponemata but it is currently felt that they are likely to belong to the genus borrelia For this reason, the inclusion of relapsing fever under "Spirochetal Diseases" is done with some license The borrelia may be seen in blood smears stained routinely with Wright's or Giemsa's stains; they are about 10 to 20 microns in length, actively motile and have several broad coils

*The incubation period* of relapsing fever about three to six days. The clinical picture the tick-borne form is characterized by a som what more severe course with more freque relapses and complications than occur in t louse-borne disease *The onset in both types* sudden with headache, remittent fever ar prostration The primary stage lasts sever days to a week and subsides spontaneousl With each succeeding attack—usually one, tw or more occur—*the symptoms become less se*vere Specific antibodies are present which de crease in titer after the paroxysms subsid The mortality rate is approximately 5 per cen Pneumonia, anemia, jaundice, meningitis, an iritis are the common complications, in additio to *focal interstitial nephritis* and *glomerulitis* The organisms may be demonstrated in bot glomeruli and tubules, with or without slight associated lesions (plate 165A, B).

## Leptospirosis

Leptospirosis or Weil's disease is an acute infectious disease of dogs and humans caused by the spirochete, *Leptospira icterohemorrhagiae* In humans the infection is highly virulent and the mortality is about 30 per cent Undoubtedly the incidence of the disease is greater than generally indicated because Weil's disease is mistaken for other forms of hepatitis with jaundice. The rat is the reservoir of *Leptospira icterohemorrhagiae* but does not contract the

with the excreta of infected rats.

*The clinical features* of Weil's disease are those of severe infectious hepatitis, often with a complicating renal insufficiency The incubation period is about 10 days after which headache, fever, prostration and myalgia especially of calf muscles occur. A hemorrhagic tendency is common in this initial stage during which the organisms may be recovered from the blood. This septicemic stage is followed by progressive recovery in the mild cases, but in the more severe ones jaundice develops frequently to an extreme degree With the jaundice *there may* be associated the complete clinical syndrome of

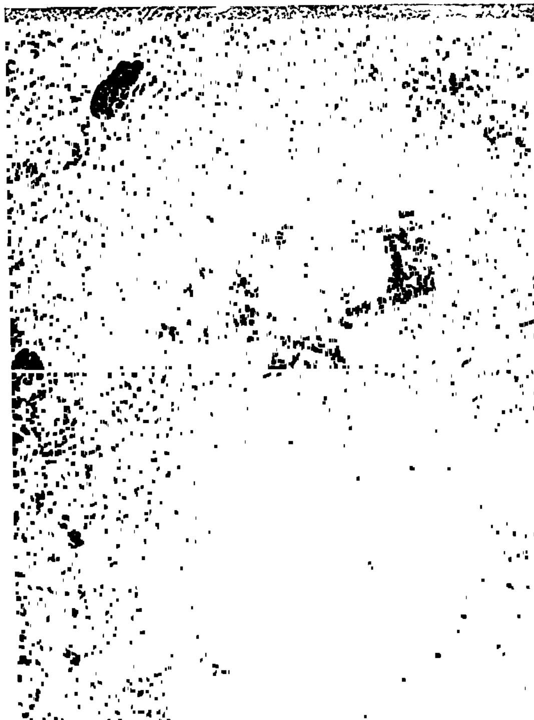


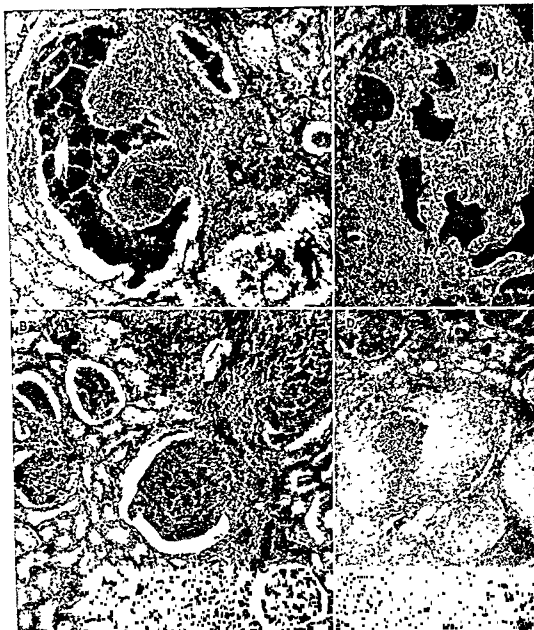
FIG A *Caseous tuberculosis*, recent hematogenous dissemination with marked caseous component

FIG B *Healed tubercle* of kidney with central calcareous degeneration at right of photomicrograph




FIG A *Sarcoidosis of kidney* from a white female (aged 42) with classical generalized sarcoidosis There was no renal dysfunction

FIG B *Renal sarcoidosis* with fragments of a Schaumann body in a tubercle. (From same case illustrated in figure A )




FIGS A AND B *Syphilitic (?) nephritis*, characterized by patches mainly of lymphocytes which bulge the walls of distal convoluted tubules into their lumens Cellular debris and cholesterol needles occupy the lumen The lesion is found in the secondary stage of syphilis, according to Rich No spirochetes have been demonstrated in the lesions Courtesy of Dr A R Rich (A F I P Acc 109302)

FIGS C AND D *Lesions of chronic nonspecific* [illegible]

though the incidence of the change appears considerably higher in syphilitics

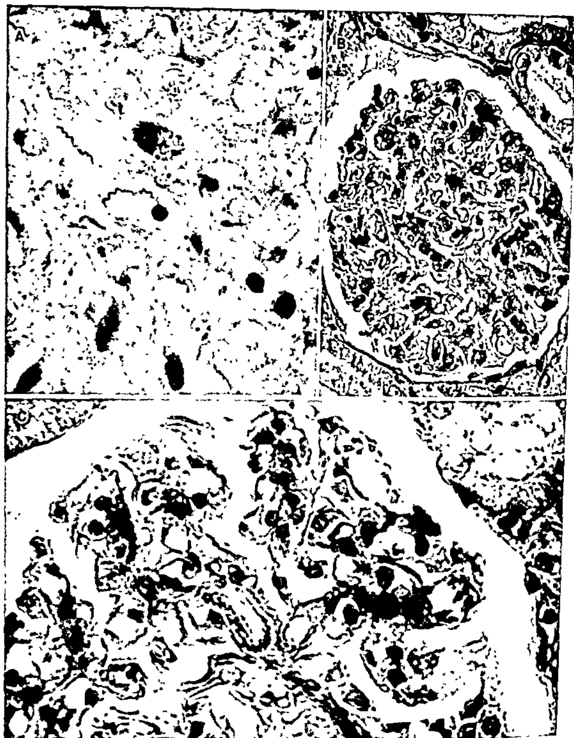



FIG. A *Treponemas of relapsing fever* in glomerular capillaries (Warthin-Starry stain)

FIG B *Mild proliferative glomerulitis* in relapsing fever.

FIG C. *Larva of canine filaria* in glomerulus




FIG A *Interstitial nephritis* due to infection of human by *Leptospira icterohemorrhagiae*

FIG B *Focal interstitial nephritis* from a syphilitic The picture contrasts with that of figure A

FIG C *Leptospira icterohemorrhagiae* in proximal convoluted tubule of human kidney (Warthin-Starry stain) (A F I P Acc. 64526)

FIG D *Leptospira canicola* in proximal convoluted tubule of kidney of a dog (Warthin Starry stain)

hemoglobinuric nephrosis or severe cholemic nephrosis with oliguria or anuria and mounting azotemia. Renal insufficiency and jaundice are present between the *ninth and sixteenth days* and are accompanied by a high titer of specific antibodies Iridocyclitis, meningitis and even leptospiral endocarditis may complicate the *convalescence It is of interest in connection* with the renal picture, which may simulate hemoglobinuric nephrosis clinically and pathologically, that necrosis of voluntary muscle is *reported as a common finding in Weil's disease* (Sheldon). The common incidence of the myositis has been recently disputed, however. The hepatitis which is usually remarkably incon*spicuous histologically, in contrast to severe* symptoms, is responsible for the cholemic nephrosis, of course, but it may also contribute to the occasional instance of hemoglobinuric *nephrosis after the, as yet, unclarified manner* of other types of hepatitis

In addition to cholemic and hemoglobinuric nephrosis, there commonly occurs a patchy in*terstitial nephritis, generally most marked in* the corticomedullary region but also involving the cortex and medulla proper. The inflammatory cells consist predominantly of plasma cells *along with* lymphocytes and basophilic and acidophilic histiocytes In dogs that remain carriers of leptospira, the interstitial nephritis persists for a long period and, in some instances, appears to be replaced by scars Whether a corresponding lesion occurs in the human kidneys is not known. Frequently, onto the focal interstitial nephritis there is superimposed a cholemic (less frequently hemoglobinuric) nephrosis with serious compromise of renal function. Characteristic "C" or "S" shaped treponemas may be in the tubular lumens, particularly of the [illegible]

## The Rickettsial Diseases

### *Introduction*

The principal rickettsial diseases are. (1) epidemic, louse-borne typhus fever and Brill's disease, (2) endemic (murine) flea-borne typhus, (3) the spotted fever, tick-borne group, (4) the tsutsugamushi fever or scrub typhus *group borne by the larval mite*, and (5) a miscellaneous group including "Q" fever. The vaccines and the antibiotics, chloromycetin and aureomycin, have eliminated much of the dread *of these diseases*, which, in the past, have been responsible for literally millions of fatalities

The causative organism is one of a variety of rickettsias which are identified by tests of their *diverse antigenic properties, including* the complement-fixation tests, the direct rickettsial agglutination and the Weil-Felix reaction against the OX19, OX2 and OXK strains of *B. proteus The rickettsias are transmitted by ticks, fleas or* larval mites, their reservoirs are mice, rats or bandicoots. Brill's disease, murine typhus, Rocky Mountain spotted fever, rickettsialpox, *and "Q" fever still occur in the United States* The epidemic, louse-borne typhus is a disease known to be smoldering in the Near East chiefly, but is present elsewhere including Mexico The *tsutsugamushi group* is *found* in the Far East as is also "Q" fever. The spotted fever group of diseases is present in South America, Europe and Africa, as well as in the United States.

### *Renal Picture*

Renal complications have been observed in the epidemic typhus fever, Rocky Mountain spotted fever and scrub typhus The clinical picture in these diseases is essentially similar and consists of headache, chills, fever, prostration, followed by a maculo-papular rash and, in severe cases, insomnia, delirium, convulsions, shock and vasomotor collapse. In spotted fever, hemorrhagic necrosis of the scrotum may occur; in scrub typhus, a primary lesion or eschar develops at the site in which the rickettsias are inoculated by the mite Azotemia with oliguria is common in each of these diseases, especially in epidemic typhus (Yeomans et al.). Clinical *investigators have attributed the azotemia to* liver damage secondary to vascular involvement This conclusion is completely without histologic foundation (Allen and Spitz).




FIGS A AND B *Glomerulonephritis of epidemic (louse-borne) typhus fever* with the hemorrhagic mottling commonly found in the kidneys of the typhus fevers

FIGS C AND D *Acute diffuse proliferative glomerulonephritis* of epidemic (louse-borne) typhus, a common finding in the typhus fevers (Am J Path *21* 603-681, 1945)




FIG A *Glomerulonephritis* of Rocky Mountain spotted fever.

FIG B *Arteritis and periarteritis* in myocardium from a case of epidemic typhus fever

FIG C *Arteritis in kidney* in Rocky Mountain spotted fever The renal arteritis is infrequent and rarely is responsible for renal dysfunction in any of the typhus fevers (Am. J. Path 21. 603-681, 45).




FIG A *Acute interstitial nephritis* in scrub typhus

FIG B *Acute diffuse glomerulonephritis* of scrub typhus

FIG C *Phlebitis of renal interlobar vein* in scrub typhus Arteritis, except for the skin, is extremely rare in scrub typhus (Am J Path 21 603-631, 1945).

# PLATE 170. Typhus Fevers: Scrub Typhus (Tsutsugamushi Disease)




Fig A *Characteristic concentration of mononuclear cells* (lymphocytes, plasma cells and histiocytes) in peritubular capillaries The peripheral blood count showed merely a mild lymphopenia so that these cells represent a selective localization probably prior to interstitial deposition A similar picture is found in nephritis from other causes (Am J Path *21* 603-681, 1945).

Fig B *Tubular degeneration and regeneration* in a roximal tubule of kidney in scrub typhus A mitotic gure is seen This degree of change is unusual (Am Path *21* 603-681, 1945)

Fig C. *Rickettsias* of scrub typhus from splenic smear (Giemsa stain)




FIG A *Marked interstitial nephritis* of renal medulla from a case of hemorrhagic smallpox The inflammatory cells are almost exclusively lymphocytes

FIG B *Hemorrhage in renal pelvis* from a case of hemorrhagic smallpox The kidney participates in the generalized hemorrhagic diathesis Such a massive pelvic hemorrhage might simulate a neoplasm in a pyelographic roentgenogram

Focal interstitial nephritis characterized by lymphocytes, plasma cells and basophilic histiocytes is common in all of the typhus fevers. It is quite the same quality of focal interstitial nephritis that is present in other infections, such as smallpox (plate 171A) and leptospirosis (plate 166A)

The kidneys, in a high percentage of cases show an early, reversible, but definite, acute diffuse proliferative glomerulonephritis This change was found in 30 per cent of cases of scrub typhus, 50 per cent of cases of Rocky Mountain spotted fever, and 78 per cent of those with epidemic typhus The glomerular lesions resemble those of acute diffuse glomerulonephritis described by Bell in 64 8 per cent of instances of subacute bacterial endocarditis. Cafferena found acute diffuse glomerulonephritis in 67.5 per cent of cases of epidemic typhus fever, a figure along with our own, that is much higher than those generally recorded (plates 167–170) (Allen and Spitz)

Despite the deeply entrenched cliché that the typhus fevers are yet another example of diffuse vascular disease, it must be emphasized that no extraglomerular lesions of renal vessels were found in the personal examination of over three hundred cases of scrub typhus. In epidemic typhus and Rocky Mountain spotted fever, visceral arteritis may be found (plate 168B, C) but the process is usually so sparse as to be functionally insignificant for all practical purposes, with the exception of the brain This same disparity obtains between quantitative vascular involvement of viscera and the grave physiologic derangement attributed to the arteritis by most investigators of the typhus fevers. As a matter of fact, visceral arteritis in scrub typhus is almost always completely absent, nevertheless, in these cases, the clinical picture of sepsis is basically similar to that of epidemic typhus and Rocky Mountain spotted fever in which more frequent but still isolated arteritis is histologically overemphasized very much as it is in diffuse lupus erythematosus and scleroderma

lesions in the kidneys of cases with spotted fever and epidemic typhus. As has been previously indicated (Allen and Spitz) the visceral lesions of the typhus fevers—e.g, the interstitial pneumonitis, the myocarditis, the necrosis of lymph nodes, the interstitial nephritis, the diffuse glomerulonephritis—are in all likelihood a reaction to allergens or toxins from the rickettsias rather than to the direct local action of the organisms themselves. As mentioned, the principles of allergy that apply to bacteria obtain just as intimately in the case of rickettsias and viruses.

### Fungus Diseases

The fungi, including *Coccidioides immitis, Blastomyces dermatitidis, Histoplasma capsulatum, Cryptococcus neoformans* and *Actinomyces bovis*, may involve the kidney but are not responsible for any significant renal insufficiency with the occasional exception of the last named

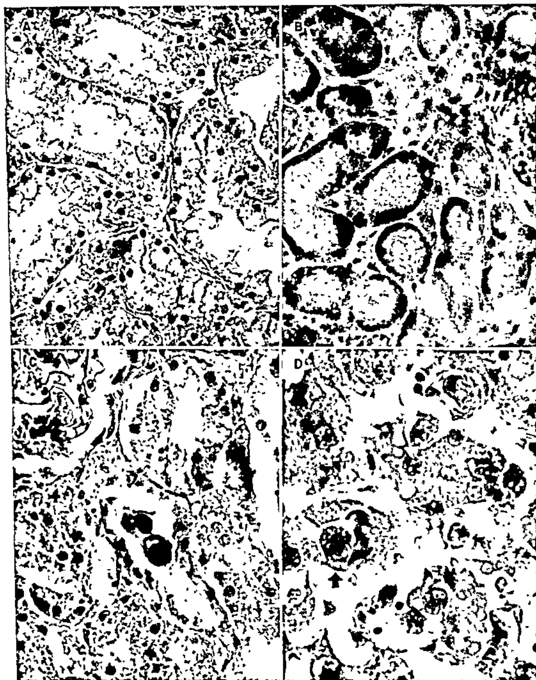
#### *Coccidioidomycosis*

Coccidioidomycosis occurs principally in the west and southwest of the United States. The first case in this country was described in 1896. The causative organism is the nonbudding, endosporulating, doubly contoured, variable-sized fungus, *Coccidioides immitis.*

Two essential clinical pictures occur.

1. An evanescent self-limited *pneumonitis* known also as Valley fever, dust fever, or San Joaquin Valley fever. This entity probably represents the entire reaction in a majority of cases and is associated often with *erythema nodosum* The allergic nature of this phase of coccidioidomycosis is strongly suggested. Skin tests and complement fixation tests are strongly positive in this phase of pneumonitis The organisms are not recovered in the sputum. No renal complications are attributed to this response, but the occurrence of occasional concomitant cases of acute glomerulonephritis would not be surprising.

2. The far more serious form of coccidioidomycosis is the *granulomatous stage*, representing endogenous spread. About 1 of every 500 cases of what is initially apparently allergic pneumonitis progresses to the fatal dissemi-




FIGS A AND B *Lipid vacuolization of epithelium of proximal tubules* in kidney of yellow fever (Sudan III stain in figure B)

FIG C *Anisotropic yellowish green crystals* in distal convoluted tubules in yellow fever These crystals resemble leucine

FIG D *Councilman bodies* (arrow) in hepatic cells in yellow fever.




FIG A *Coccidioidomycosis of kidney* The greyish-white nodules represent coccidioidal granulomas, resulting from hematogenous dissemination

FIG B *Coccidioidal granuloma* of kidney The granuloma consists of lymphocytes, macrophages, and giant cells with spherules of *Coccidioides immitis.*

FIG C *Spherules of Coccidioides immitis* present in granuloma of figure B

FIG. D *Coccidioidal spherules* showing double contour of capsule which encloses typical endospores Budding does not occur

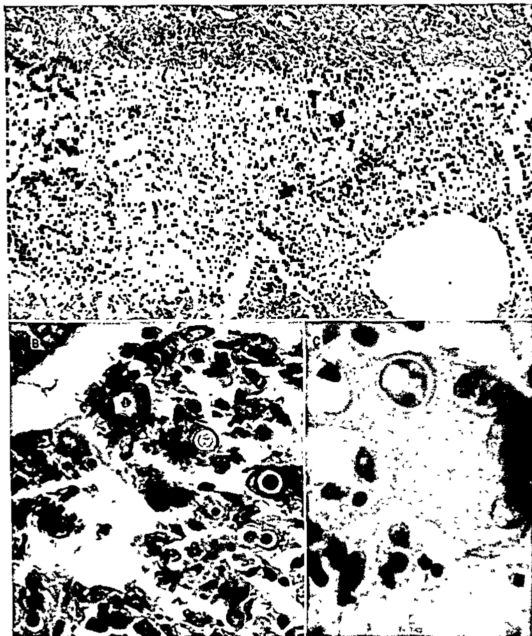



FIG A *Blastomycotic giant cell granulomas* in association with acute diffuse glomerulonephritis as evidenced by the glomerulus at the left Higher magnifications are in figures A and B

FIG B *Blastomycotic spores*, with budding No endosporulation occurs in these cells in contrast to those of coccidioides

FIG C *Spores of Blastomyces dermatitidis* with doubly contoured capsule in a giant cell




Fig A *Actinomycotic granuloma* with the ray fungus at the right

Fig B *Actinomyces bovis* under high magnification (paraffin section) The characteristic peripheral (acid-fast) clubs as well as the polymorphonuclear leukocytic reaction are seen

Fig C *Smear of actinomyces* showing the typical branching forms (Gram stain).

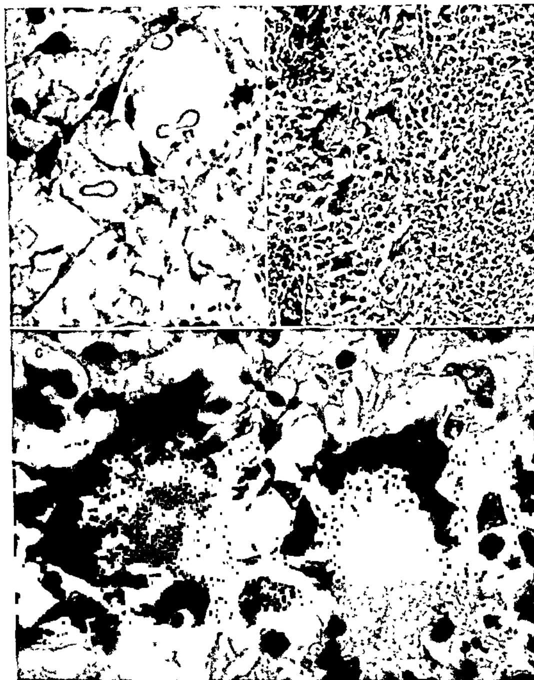



FIG A *Torula (Cryptococcus hominis)* may infect the kidney Budding forms and large gelatinous capsules are shown

FIG B *Renal histoplasmosis* showing giant cell granulomas

FIG C *Histoplasma capsulatum* in giant cells, from renal histoplasmosis illustrated in figure B




FIG A *Echinococcus cyst* showing dense capsules and daughter cysts

FIG B *Daughter cysts* of *Echinococcus granulosus.*

FIGS C AND D *Detailed photographs showing hooklets of scolices of echinococcus cysts*

nated granulomatous form Clinically, roentgenologically and anatomically in the gross, the granulomatous phase of the disease, in all basic respects, is indistinguishable, or almost indistinguishable from the picture of tuberculosis. Even the coccidioidin skin test, as in tuberculosis, may become negative in the terminal phase.

The renal lesions take the form of minute or coalescent, hyperplastic or necrotic, miliary tubercles (plate 173) Histologically, the tubercles can not be differentiated from those of tuberculosis except for the finding of the specific organism. The spherule of *Coccicioides immitis* is usually about 20 microns in diameter but may be several times that. The walls are doubly-contoured and may enclose several or numerous endospores or potential spherules (plate 173 C and D) Usually the spherules are localized to the Langhan's giant cells of the tubercle Occasionally nonspecific vacuoles within the giant cells may be mistaken for fungi No involvement of the renal pelves or ureter was noted in 95 cases (Forbus and Bestebreurtje)

*Blastomycosis*

Blastomycosis (Gilchrist's disease), also called North American blastomycosis in contrast to South American blastomycosis (paracoccidioidal granuloma), is another form of cutaneous deep fungus infection which may disseminate to involve any of the viscera There is reason to believe that, as with coccidioidomycosis, the skin is not the only portal of entry, the respiratory tract appears to be an occasional primary site from which cutaneous and visceral systemization may follow An evanescent pulmonary phase corresponding to the Valley fever of coccicioidomycosis has not been identified

The renal histologic lesions are quite like those of coccidioidomycosis The organism of *Blastomyces dermatitidis* is a small, 5 to 12 micron, yeastlike, budding, nonendosporulating spherule usually found within giant cells Plate 174 illustrates a kidney with an acute diffuse glomerulonephritis in addition to the hematogenous granulomas of blastomycosis The possibility of the pathogenesis of the glomerulonephritis being allergic in nature and dependent on the blastomyces certainly cannot be gainsaid The tubercles of blastomycosis tend to become purulent and necrotic These tubercles may be indistinguishable from those of coccidioidomycosis or tuberculosis without demonstration of the etiologic organisms

*South American Blastomycosis*

South American blastomycosis is limited chiefly to Brazil, Uruguay, Argentina, Venezuela and Peru The disease is caused by the organism *Paracoccidioides brasiliensis* The symptomatology and visceral lesions are similar to those of North American blastomycosis The organisms (*Paracoccidioides brasiliensis*) are fairly large, 25 to 30 microns in diameter, and show multiple peripheral buds Endosporulation does not occur

*Actinomycosis*

Actinomycosis, or lumpy jaw, is another widespread fungal granulomatous disease associated with visceral lesions The causative organism is *Actinomyces bovis* or other species of this genus The organism is usually introduced into the buccal cavity, but the skin of other parts of the body may be the portal of entry In addition many instances of visceral involvement follow contamination of the peritoneal cavity during an appendectomy or as a result of spontaneous rupture of the appendix As in the skin, burrowing sinuses steadily invade one viscus after another and make of the abdominal viscera an almost indissectable mass of riddled, matted organs The kidneys, of course, participate in this process and extensive abscesses with pyelonephritis may occur Grossly, the granulation tissue is likely to be distinctively yellowish because of the numerous lipid filled macrophages in the granulomas The grossly visible yellowish grey "sulfur" granules are several millimeters in diameter, these contain the ray fungus (plate 175)

Histologically, the ray fungus is composed of central Gram-positive masses of tightly entangled branching mycelial threads with a radial arrangement near the periphery and

clubbed ends at the tips. The ray fungus usually lies in a small pool of purulent exudate surrounded by granulation tissue with abundant histiocytes filled with fat The previous uniformly fatal prognosis of this disease has been radically changed with the use, particularly, of the antibiotic, aureomycin

### *Torulosis of Kidney*

Torulosis is a chronic infection produced by a yeastlike fungus named *Cryptococcus neoformans* or *Torula histolytica.* The disease is also known as European blastomycosis The organisms are oval or spherical, budding, thick-walled cells surrounded by a mucicarminophilic gelatinous capsule (plate 176A) The organisms average about 6 to 12 microns in diameter, and they grow well on Sabouraud's agar or meat extract dextrose agar

The organisms have a special affinity for the central nervous system, causing a chronic meningitis and cystic encephalitis. The portal of entry is probably the respiratory tract and the lungs may be involved. The kidneys are rarely affected in the spontaneous disease although renal infection occurs often in rats inoculated intraperitoneally with torulae (Jones). In isolated instances, visceral involvement in humans is found in the absence of cranial involvement.

The appearance of the kidneys grossly may resemble that seen in miliary tuberculosis or miliary coccidioidomycosis because of the scattered distribution of small grey nodules Histologically, the fungi are found in glomeruli, tubules, or interstitium Cellular reaction about the organisms may be absent or sparse or there may be a cyst or a nodule of lymphocytes and histiocytes which rarely are arranged in tubercle formation Masses of the fungus may dilate individual tubules and in such instances, organisms are recoverable from the urine. Inoculation of mice by suspicious material reproduces easily identifiable lesions in many organs As with blastomycosis and coccidioidomycosis, renal insufficiency is rarely caused by direct renal invasion of the fungi.

### *Histoplasmosis*

Histoplasmosis (Darling's disease), caused by *Histoplasma capsulatum* and other species, is a generalized mycosis characterized by fever, anemia, leukopenia, splenomegaly, hepatomegaly, pulmonic involvement and lymphadenitis. Renal involvement is infrequent. Involvement of the cardiac valves, adrenals, bones, and intestine with prominent ulceration may occur. It is felt that some of the calcific nodules generally dismissed as healed tuberculosis may actually represent healed granulomas of histoplasmosis Such nodules, active or calcified, may be miliary and may simulate miliary tuberculosis of the lungs Similar tubercles occur in the kidney without major dysfunction.

Histologically the lesions are formed of necrotic, caseous appearing centers with giant cells and various mononuclear cells at the periphery The organisms are present particularly in the giant cells (plate 176B, C), but they also lie free or in single histiocytes These fungi may be mistaken for leishmania but *Histoplasma capsulatum* is slightly larger, averaging 3 microns in diameter and has a more prominent nucleus located slightly off center. The kinetoplast and parabasal body of leishmania are, of course, not present.

## ECHINOCOCCOSIS

### *Life History of Echinococcus granulosus*

The natural habitat of *Echinococcus granulosus* (*Taenia echinococcus*) is the intestine of the dog Man (as well as sheep and cattle) acquire the infection by ingesting the ova, and the dogs, in turn, become infected from eating the viscera of sheep and cattle which contain fertile larval cysts.

The ova ingested by man hatch into hooked embryos which penetrate the portal circulation. The few larvae that are not filtered out by the liver may reach the lungs, brain, bones and other organs including the kidneys The infection remains symptomatically latent for a long time in the final organ of localization. The immediate reaction of the host's renal tissue is active inflammation, presumably an allergic response to the larva This reaction subsides as the leak of hydatid fluid becomes contained in




FIG A *Acute diffuse glomerulonephritis* in quartan malaria

FIGS B AND C *Tubular alteration in malaria* Figure B (*P falciparum*) shows necrosis of epithelium of distal convoluted tubules in blackwater fever In figure C the epithelium of proximal convoluted tubules is swollen with colloid or hyaline droplets or granules (quartan malaria)




FIG A *Malarial (quartan) glomerulonephritis* showing fatty vacuolization of the epithelium of the proximal convoluted tubules The patient presented a picture of the nephrotic syndrome

FIG B *Malarial pigment* (falciparum) in endothelial cells of glomerulus (arrows).

A



B

Fig A. *Kidney from a case of blackwater fever (P falciparum)* showing cortical swelling and congestion of the medulla

Fig. B *Hemoglobinuric nephrosis* of blackwater fever (*P falciparum*)

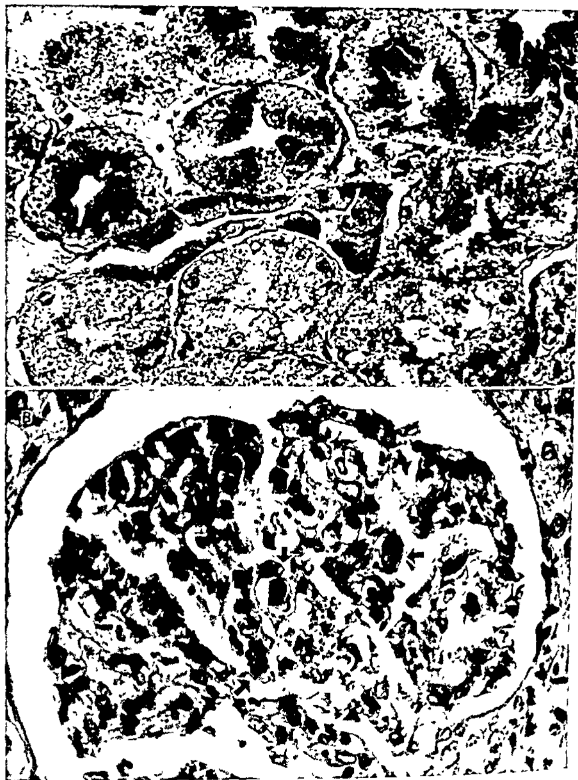



FIG A *Malarial (quartan) glomerulonephritis* showing fatty vacuolization of the epithelium of the proximal convoluted tubules The patient presented a picture of the nephrotic syndrome

FIG B *Malarial pigment* (falciparum) in endothelial cells of glomerulus (arrows).

A



FIG A *Kidney from a case of blackwater fever (P falciparum)* showing cortical swelling and congestion of the medulla

FIG B *Hemoglobinuric nephrosis* of blackwater fever (*P. falciparum*)

the adventitious nonspecific capsule of granulation tissue which encases a specific laminated hyalinized translucent wall. This laminated membrane is lined by germinal epithelium (plate 177). *Frequently the cyst is unilocular* and sterile, that is, without daughter cysts. The fertile cysts are those in which the germinal epithelium has given rise to brood vesicles lined by a single layer of cells from the inner surface of which scolices are formed. If the brood capsules are ruptured, the scolices are found in the hydatid fluid where they are referred to as "hydatid sand" Endogenous daughter cysts are formed from the invaginations of the wall of the mother cyst Evagination of the same wall produces exogenous daughter cysts which may become separated from the mother cyst to form secondary hydatid cysts. A scolex consists of an anterior rostellar portion with four suckers and a double ring of hooklets The scolices are characterized by highly refractile particles of carbonate of lime which often appear doubly contoured or laminated (plate 177C, D)

### *Clinical Picture*

The renal involvement is often part of a generalized echinococcosis Local symptoms are the result of pressure of the cysts An instance of malignant hypertension secondary to involvement of a renal artery has been reported (Davison) Adherence to adjacent structures and rupture may lead to grave anaphylactic complications. Some of the cysts become sterile, their growth ceases and they remain symptomatically latent Others become inert through the effects of inflammatory and degenerative calcific changes. Calcification, *per se*, does not preclude vitality of the parasites (Reay and Rolleston) Those cysts that continue to grow may show the relentless expansion of a neoplasm

### *Diagnosis*

*The echinococcus cysts of the kidney are* usually single and vary from a few centimeters to a huge mass filling the accessible retroperitoneal space. The cysts occasionally rupture into the pelvis producing the picture of renal colic and pyelonephritis as the scolices and daughter cysts reach the bladder These attacks may recur as the primary cyst closes and reopens Rupture of the cyst into the pelvis may eliminate the daughter cysts and result in sterilization of the primary cyst. In the opened cyst, examination of the urine may reveal scolices and hooklets as well as pieces of laminated membrane. *Palpation of a thrill by bimanual* examination of the cyst is rare. Calcification of the wall of the cyst may be noted in roentgenograms as well as a "spider leg" deformity of the pelvis in urograms. Complement fixation and intradermal skin tests may be useful for diagnosis unless the cysts are so inactive that insufficient amounts of antigen are absorbed The differential diagnosis includes neoplasms, other types of cysts, renal calculi, tuberculosis, hydronephrosis and acute abdominal diseases

### References


ALBRIGHT, F, AND REIFENSTEIN, E C, JR The Parathyroid Glands and Metabolic Bone Disease Baltimore, Williams & Wilkins, 1948

ALLEN, A C, AND SPITZ, SOPHIE A comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases Am J Path 21: 603–682, 1945

ASH, J E, AND SPITZ, SOPHIE *Pathology of Tropical* Diseases An Atlas Philadelphia, Saunders, 1945

ASHE, W F, PRATT-THOMAS, H R, AND KUMPE, [illegible]

BAK [illegible]

BELL, E T Glomerular lesions associated with endocarditis Am J Path 8: 639–664, 1932.

CAFFERENA, F M Pathologisch-anatomisch Beteiligung der Nieren beim Fleckfieber (Abstract) Zentralbl f allg Path. u path Anat 67: 203, 1937

CRONE, J T, DEGROAT, A F, AND WAHLIN, J G *Torula infection Am J Path* 13, 863–879, 1937.

DAVISON, J Malignant hypertension associated with hydatid disease of the kidney. *J. Path and Bact* 53, 207–212, 1941

FISHBERG, A M · Hypertension and Nephritis Philadelphia, Lea and Febiger, 1939

FORBUS, W D, AND BESTEBREURTJE, A D Coccidioidomycosis. a study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease Mil Surg 99. 653–719, 1946

HAGER, B H. Renal hydatid (renal echinococcosis) Chapter XIV in H Cabot, Modern Urology, Vol II, 3rd ed Philadelphia, Lea and Febiger, 1936

HERMANN, C, AND MARR, W. L Clinical nephropathies, new case and survey of reported cases Am J Syph & Neurol 19: 1-29, 1935

HEYMAN, A, AND BROWN, C E Acute syphilitic nephrosis, report of a case Ann Int Med 25: 728-731, 1946

HOLLISTER, W F, AND HARRELL, G T Generalized sarcoidosis of Boeck accompanied with tuberculosis and streptococcic bacteremia, clinicopathologic study with autopsy and animal inoculations Arch Path 31: 178-188, 1941

HOLTEN, C Nephritis caused by tuberculosis Acta med Scandinav 61: 107-142, 1924

JAFFÉ, R H The pathology of pulmonary tuberculosis Chapter 4 in Goldberg, B, Clinical Tuberculosis Philadelphia, F A Davis Co, 1937.

JEGHERS, H J, HOUGHTON, J D, AND FOLEY, J A Weil's disease, report of a case and review of recent literature Arch Path 20: 447-476, 1935

JONES, E L Torula infection of the nasopharynx South M J 20. 120-126, 1927

KLINEFELTER, H F, JR, AND SALLEY, S M Sarcoidosis simulating glomerulonephritis Bull Johns Hopkins Hosp 79: 333-341, 1946

LONGCOPE, W T Sarcoidosis, or Besnier-Boeck-Schaumann disease J A M A 117: 1321-1327, 1941

MELENEY, H E Histoplasmosis (reticuloendothelial cytomycosis) a review, with mention of 13 unpublished cases Am J Trop Med 20: 603-616, 1940

MUNK, FR Pathologie und Klinik der Nierenerkrankungen (Nephrosen, Nephritiden, und Schrumpfnieren) 2nd ed Berlin and Vienna, Urban and Schwarzenberg, 1925

PATTON, E W, AND CORLETTE, M B Three cases of acute syphilitic nephrosis in adults Ann Int Med 14 1975-1980, 1941

RANKE, K E Primare, sekundare und tertiare Tuberculose des Menschen, Munchen med Wchnschr 64: 305-308, 1917

REAY, E R, AND ROLLESTON, G L: Diagnosis of hydatid cyst of the kidney J Urol 64: 26-52, 1950

RICH, A R Pathology of 19 cases of peculiar and specific form of nephritis associated with acquired syphilis Bull Johns Hopkins Hosp 50: 357-382, 1932

—— The Pathogenesis of Tuberculosis Springfield, Ill, C C Thomas, 1944, pp 318, 473

SCOTT, V, AND CLARK, E G Syphilitic nephrosis as a manifestation of a renal Herxheimer reaction following penicillin therapy for early syphilis Case report Am J Syph Gonor. and Ven Dis 30: 463-467, 1946

SCULLY, J P, AND YAMAZAKI, J N Congenital syphilitic nephrosis successfully treated with penicillin Am J Dis Child 77. 652-658, 1949

SHELDON, W H Lesions of the muscle in spirochaetal jaundice (Weil's disease, spirochetosis icterohemorrhagica) Arch Int Med 75. 119-124, 1945

SPENCER, J, AND WARREN, S Boeck's sarcoid, report of a case, with clinical diagnosis confirmed at autopsy Arch Int Med 62: 285-296, 1938

SUSSMAN, R M, AND KAYDEN, H J Renal insufficiency due to paroxysmal cold hemoglobinuria Arch Int Med 82. 598-610, 1948

TUCKER, H A Penicillin treatment of acute syphilitic nephrosis and iritis, report of a case Am J M Sc 211: 718-722, 1946

WATTS, J W Torula infection A review and report of 2 cases Am J Path 8: 167-192, 1932

YAMPOLSKY, J, AND MULLINS, D F, JR Acute glomerular nephritis in an infant with congenital syphilis Am J Dis Child 69: 163-172, 1945

YEOMANS, A, AND OTHERS The therapeutic effect of para-aminobenzoic acid in louse borne typhus fever J A M A 126: 349-356, 1944

# 10. Pyelonephritis

*Introduction*

PYELONEPHRITIS, in one of its stages, is the most common renal lesion found at autopsy. This fact is hardly surprising in view of the large and diversified number of conditions that lead to pyelonephritis. These conditions include, along the hematogenous route, the many varieties and degrees of sepsis with renal localization, and, by the route of retrograde ureteral ascension, there is the long list of causes of obstruction of the lower urinary tract. Many instances of pyelonephritis are latent and discovered only at autopsy. Nevertheless, of the chief causes of contracted kidney, chronic pyelonephritis is more common than chronic glomerulonephritis and somewhat less common than benign nephrosclerosis.

Pyelonephritis, exclusive of the specific granulomatous diseases, such as tuberculosis, may be divided by pathogenesis and chronicity into:

- Hematogenous pyelonephritis
  - Acute
  - Subacute
  - Chronic
- Ascending pyelonephritis
  - Acute
  - Subacute
  - Chronic

There are observers (Weiss and Parker) who feel that it is impossible to know in a given case by which route the organisms reach the kidney. There are others (Mallory, Crane and Edwards) who are convinced that, even in the presence of ureteral obstruction, pyelonephritis is not effected by retrograde ascension of organisms, but rather that the organisms reach the kidney always by the lymphatic vessels, or by the blood stream. This concept may obtain in tuberculous nephritis, but its blanket application to suppurative pyelonephritis, in the presence of suppurative cystitis, ureteritis, and pyelitis, is doubted.

A major role of *pyelo-venous reflux* and *pyelo-interstitial reflux* in the development of pyelonephritis has also to be proved. It is unquestionably true that retrograde pyelograms occasionally reveal radio-opaque material outside the calyceal and tubular system, in the interstitium, or in structures interpreted as veins. Tears of the mucosa by abnormal pelvic distention may account for some of the pictures, but a normal pyelo-venous communication is assumed to exist (Hinman). However, the relative paucity of renal pyelophlebitis, and particularly its distribution with regard to the foci of suppuration in acute ascending pyelonephritis, does not indicate a primary role of these veins in the dissemination of the renal inflammation. It is difficult to doubt that pyelonephritis by ascending spread of organisms does occur in addition to hematogenous pyelonephritis and that the two may be distinguishable in the acute stage, the scanty evidence for lymphangitic pyelonephritis does not seem to entitle it to the prominence which some have attached to it.

*Hematogenous Pyelonephritis*

In the absence of obstruction of the urinary tract, pyelonephritis is assumed to be hematogenous. Weiss and Parker indicate, however, that physiologic obstruction may exert an effect equivalent to organic obstruction; on the other hand, the mere presence of organic obstruction not only does not preclude the hematogenous entry of organisms into the kidney, but actually renders such a kidney more susceptible to hematogenous localization during a bacteremia. Nevertheless, the fact that during an operation on the lower urinary tract, or following infection of this region, or even following catheterization of the urinary bladder, organisms may gain access to the blood stream and thence, in some instances, to the kidney, does not by any means disprove that ureteral ascension of infection may also occur.

*Obstructive Pyelonephritis*

Obstructive pyelonephritis is a complication of pregnancy, ureteral calculi, strictures, aber-

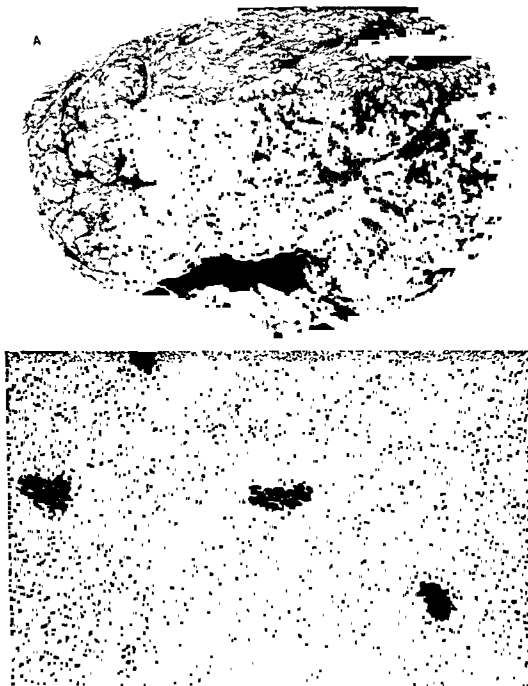



FIG A *Acute hematogenous pyelonephritis* in a case of *Staphylococcus aureus* septicemia The light areas represent coalescent abscesses

FIG B "*Excretion*" abscesses at cortico medullary junction in acute hematogenous pyelonephritis The black masses are clumps of staphylococci The glomeruli show no histologic change. The patient was a 22 year old man with a *Staphylococcus aureus* sepsis







FIG. A *Acute hematogenous pyelonephritis* in staphylococcic septicemia The diffusely scattered white dots represent abscesses which show no selective distribution

FIG B. *"Excretion" abscesses* of acute hematogenous pyelonephritis

FIG C *Purulent exudate* in collecting tubules in acute hematogenous pyelonephritis This field alone could not be distinguished from acute *ascending* pyelonephritis

rant vessels, or neoplasms, metastatic or contiguous invasion of ureters or bladder by carcinoma of the rectum, uterus, or adnexae; hypertrophy or carcinoma of the prostate gland; tumors of the bladder, and spinal cord lesions. Acute pyelonephritis is particularly common in children, during pregnancy, and in old age. Banal chronic pyelonephritis in children, without any specific lesions of glomeruli or tubules, is responsible for renal rickets in a high percentage of cases (page 375). Robertson has stated that "almost every pregnant woman develops ureterectasis and pyelectasis" with urinary stasis during the second half of the gestational period, and about 1 to 6 per cent develop infections

In from 60 to 80 per cent of cases, *Escherichia coli* is responsible for the infection; in the remainder, the organisms are *Aerobacter aerogenes*, *Streptococcus fecalis*, *Staphylococcus aureus*, and the genera proteus and pseudomonas. Bacteriuria may exist without any other evidence of pyelonephritis It is obvious that the organisms may reach the blood stream secondary to an ascending pyelonephritis, just as they may secondary to ascending cholangitis following choledocholithiasis and suppurative choledochitis At times, such bacteremia has been misinterpreted as cause rather than effect of ascending suppurative obstructive pyelonephritis

### *Clinical Picture of Pyelonephritis*

In the acute phase of *hematogenous* or *obstructive pyelonephritis*, there is fever, pallor, unilateral or bilateral lumbar tenderness, dysuria, tenesmus, pyuria, occasionally bacteriuria, slight to moderate anemia and other systemic signs of an acute infection The blood pressure tends to be unchanged and no azotemia is likely to occur The acute phase may subside and recur, and may result finally in the signs and symptoms of any severely contracted kidney In this chronic phase, the symptoms obviously will vary with the extent of the scarring of the renal parenchyma With advanced disease, the patient may show pallor, with some puffiness of the face but rarely with generalized edema, alkaline urine and slight hematuria The concentration and dilution capacities and the excretion of phenolsulfonphthalein may be impaired. Hypertension and azotemia may be present for years and may be characterized by considerable fluctuation Weiss and Parker cite the case of chronic pyelonephritis that recovered from uremic pericarditis with adequate renal function for several years afterwards.

### *Pathology of Acute Hematogenous Pyelonephritis*

#### *Gross appearance*

In acute hematogenous pyelonephritis, there are gross foci of suppuration distributed haphazardly chiefly through the cortex of the kidneys (plates 181, 182, 183) Often there is a rim of congestion about the yellowish-grey abscesses The suppuration may present also as wedge-shaped infarcts with bases toward the cortical surface This is the "pyemic kidney" of acute hematogenous or suppurative pyelonephritis Occasionally the lesions may take the form of a multilocular abscess, or a honeycombed cluster of small abscesses, which are referred to as a *carbuncle* (plate 183C) Carbuncles are usually unilateral, and may follow a furuncle or cellulitis of the skin, or sore throat The infection may rupture through the capsule, and produce a perinephric abscess Perinephric abscesses may also arise independently of direct renal extension of suppuration through suppurative emboli, or by lymphatic spread

#### *Histologic appearance*

Histologically, there are scattered abscesses that appear to have been initiated chiefly in the glomeruli and in the lumens of the tubules, although there is usually considerable interstitial infiltrate In some cases, the abscesses are localized principally at the corticomedullary junction and contain central masses of bacteria (plate 183A) These have been called "excretion abscesses" on the apparently correct assumption that the bacteria reach the tubule by passing the glomerular filter without *visibly* injuring the glomerular capillaries On occasion, however, concomitant acute diffuse glomerulonephritis may accompany the suppurative hematogenous pyelonephritis (plate 183A). In such cases, the acute diffuse glomerulonephritis

## PLATE 183. Acute Suppurative Pyelonephritis (Hematogenous)

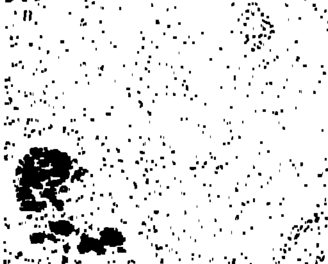





Fig A *"Excretion" abscess of acute hematogenous pyelonephritis* in association with terminal acute exudative glomerulonephritis The cluster of bacteria simulates a colony of actinomyces as shown in figure B

Fig. B *Actinomyces in abscess of kidney* showing superficial similarity of the fungus to the colony of pyogenic organisms present in figure A.

Fig. C. *Carbuncle* of the kidney shown here above may simulate a neoplasm This lesion generally is the result of a hematogenous spread of organisms from a focus elsewhere, as a furuncle of the skin

A



Fig A *Congested, dull, dilated pelvis and calyces of acute ascending pyelonephritis* associated with acute cystitis, ureteritis and hydroureter.

Fig B *Acute ascending pyelonephritis* with purulent exudate principally in the lumens of collecting tubules but also in the interstitium Ureteral obstruction with acute ureteritis was also present

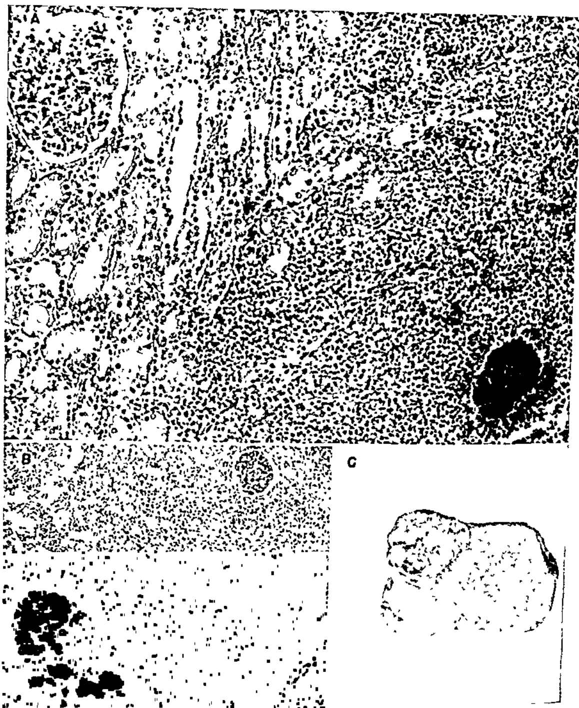



FIG A *"Excretion" abscess of acute hematogenous pyelonephritis* in association with terminal acute exudative glomerulonephritis The cluster of bacteria simulates a colony of actinomyces as shown in figure B

FIG B *Actinomyces in abscess of kidney* showing superficial similarity of the fungus to the colony of pyogenic organisms present in figure A

FIG C *Carbuncle* of the kidney shown here above may simulate a neoplasm This lesion generally is the result of a hematogenous spread of organisms from a focus elsewhere, as a furuncle of the skin

# PLATE 184. Acute Suppurative Pyelonephritis (Ascending)

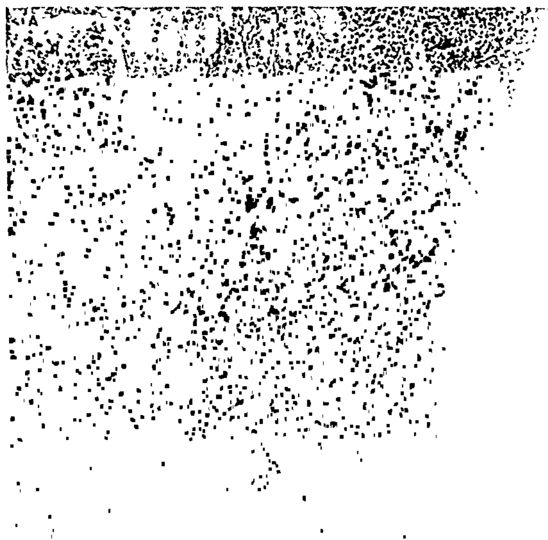
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Fig A *Congested, dull, dilated pelvis and calyces of acute ascending pyelonephritis* associated with acute cystitis, ureteritis and hydroureter

Fig B *Acute ascending pyelonephritis* with purulent exudate principally in the lumens of collecting tubules but also in the interstitium Ureteral obstruction with acute ureteritis was also present

PLATE 183. ACUTE SUPPURATIVE PYELONEPHRITIS (HEMATOGENOUS)






(Legends on facing page)

is assumed to be due, not to the direct local action of the organisms themselves, but, as in diffuse glomerulonephritis generally, to the action of the allergenic products of the organisms. Once again, this fact illustrates that more than one disease process may involve the kidney at the same time.

*Acute* hematogenous pyelonephritis is arbitrarily defined as lasting less than four months (Bell) Hematogenous subacute pyelonephritis showing resolution and organization is probably seen infrequently by the pathologist, and the chronic scarred phase is probably indistinguishable, by the pathologic picture alone, from other renal scars, especially those due to obstructive nephropathies

### *Pathology of Acute Ascending Pyelonephritis*

#### *Gross appearance*

There is usually obstruction with hydronephrosis in acute ascending pyelonephritis In the ascending type, the mucosa of the urinary tract distal to the kidney, that is, calyces, pelvis, ureter and bladder, is likely to be hemorrhagic, granular, and obviously *continuously* infected from the site of obstruction and infection, upward to the kidney The kidneys may be involved unequally, one kidney may be completely spared (plates 184, 185).

#### *Histologic appearance*

Microscopically, the picture resembles the hematogenous suppurative pyelonephritis except for the greater frequency of wedge-shaped infiltrations of the parenchyma with the apices at the calyces (plates 184, 185) The inflammatory cells are polymorphonuclear leukocytes with an admixture of lymphocytes and plasma cells Many of the glomeruli in the involved areas are destroyed.

### *Pathology of Subacute Ascending Pyelonephritis*

There is a trend to avoid the term "subacute" in the classification of diseases, including the nephritides. However, in the case of obstructive pyelonephritis there is fairly clear pathologic distinction between subacute ascending pyelonephritis on the one hand a acute and chronic ascending pyelonephritis the other

#### *Gross appearance*

In a longitudinal cut of the kidney, the more less sharp wedge of inflammatory reaction, wi its apex extending from the tip of the papil to a base beneath the cortical capsule, is ur formly pale greyish yellow and is usually rath clearly definable from the adjacent purplis brown normal parenchyma No soft areas suppuration are present and the consistency the lighter areas is not different from the re of the kidney The capsule generally is not ac herent to the cortex over these foci, the fo may be irregularly present throughout the kid ney or only one or two may be present. Th renal surface beneath the capsule is mottle yellowish grey to purplish brown correspondin respectively to the areas of inflammation an the normal or congested kidney (plate 186)

#### *Histologic appearance*

Histologically the sharp wedge of inflammatory reaction of subacute ascending pyelonephritis presents a prominent change (plates 186, 187A). Under low magnification, the compact mass of inflammatory cells may simulate the lymphosarcomatous or leukemic involvement of the kidney (plate 187B). The manner in which the inflammatory reaction fans out from the medulla to the cortex (a pattern which may be simulated by the lymphomas), the quality of the cells, the frequent fibrosis of Bowman's capsules often with unchanged malpighian tufts, and the pyelitis suggest inflammation rather than neoplasia. The inflammatory cells consist mostly of lymphocytes with scattered plasma cells and histiocytes, and a few polymorphonuclear leukocytes, the latter *may occur in clumps* in the distal tubules. In the areas of subacute pyelonephritis, the entire

FIG. A *Granular purulent inflammation* of obstructed dilated ureter and pelvis in acute ascending pyelonephritis

FIG B *Acute ascending pyelonephritis* showing wedge-shaped distribution of exudate following its ascent from pelvis

FIG. C. *Acute ascending pyelonephritis* following ureteral obstruction.




(Legends on facing page)




FIG A *Arterial nephrosclerosis* (1), *arterial and arteriolar nephrosclerosis* (2), *and subacute pyelonephritis* (3) (on the right) The latter is illustrated further in figure B

FIG B *Subacute pyelonephritis* [from kidney (3) in figure A] The lymphocytic infiltrate, atrophy of tubules, normal malpighian tufts and slight thickening of Bowman's capsule shown above precede the final wedge-shaped scarring of chronic pyelonephritis

tubular structure shows evidence of advancing atrophy in contrast to the tubular hypertrophy of adjacent nephrons of the spared parenchyma, and in contrast also to kidneys with lymphomatous infiltrate closely collaring relatively normal tubules

### *Pathology of Chronic Pyelonephritis*

*Gross appearance*

The contracted kidney of chronic pyelonephritis is not always distinguishable from shrunken kidneys due to glomerulonephritis, arterial and arteriolar sclerosis, periarteritis nodosa, and multiple healed infarcts Grossly, several features may aid in the differentiation: (1) the grey-white scarring of the pelvis and calyces, occasionally with pyelitis cystica (plate 190), (2) hydronephrosis, and (3) the presence of broad but shallow, irregular, U-shaped cortical depressions (plate 186A) The depressions tend to be U-shaped rather than V-shaped, as in infarcts, probably because of the greater rapidity of development and, often, the greater degree of atrophy in infarcted areas Obviously there are exceptions to this rule On cross section, the shallow cortical depressions may be seen as the bases of more or less wedge-shaped atrophic areas pointing to the calyces

*Histologic appearance*

Histologically, the chronic inflammation of the pelvic wall may be observed As a rule, however, there is no parallel between the degree of pelvic and parenchymal involvement in chronic pyelonephritis The more important histologic features include: (1) cortical clusters of fibrotic glomeruli, especially within the wedges of atrophic areas, (2) disproportionate thickening of Bowman's capsule in contrast to the relative integrity of the malpighian tufts, (3) the presence of many "colloid" casts in the tubules, (4) interstitial fibrosis, and (5) endarteritis obliterans (plates 188, 189) This vascular change is perhaps part and parcel of the chronic inflammatory reaction in much the same sense as is the vascular sclerosis in the base of a chronic gastric ulcer or in the vicinity of other types of chronic inflammation None of these features is by any means pathognomonic of chronic pyelonephritis, but when integrated and weighed, they help establish the diagnosis

### *Chronic Pyelonephritis and Hypertension*

The pyelonephritic kidney may develop considerable arteriolosclerosis as well as arteriosclerosis, and in about 43 to 66 per cent of patients there may be an associated hypertension (Bell, Weiss and Parker, Longcope). The average cardiac weight in chronic pyelonephritis is 450 Gm as opposed to 600 Gm. in the over-all group of malignant nephrosclerosis (Weiss and Parker). As in other kinds of renal disease with hypertension, malignant nephrosclerosis may supervene That there is a pathogenetic tie-up between chronic pyelonephritis and hypertension is certainly suggested by the very frequent association of the two. It is therefore not unlikely that there is a pathogenetic relationship between chronic pyelonephritis and arteriolosclerosis, just as there may be between chronic glomerulonephritis and arteriolosclerosis To pursue this thought one step further, when malignant nephrosclerosis occurs in association with these diseases, it is not an accidental superimposition occurring by sheer statistical chance any more than when it is superimposed onto benign nephrosclerosis Clearly this is not the same as stating that arteriolosclerosis is the cause of the hypertension

[illegible]

the relief of the hypertension (page 412) In a far greater number of instances, this procedure has been fruitless Possibly one reason for the general lack of success is the fact that arteriolar sclerosis is usually present in the "normal" kidney if the hypertension has existed for an appreciable length of time Hence, in such cases, removal of the unilateral pyelonephritic kidney leaves the contralateral kidney with the vascular change that perpetuates the elevated blood pressure initiated by the abnormal kidney Evaluation of the measure of success following nephrectomy for hypertension, at times striking, must be tempered with the realization that some relief of hypertension may occur after abdominal operations not related to the kidney (Volini and Flaxman)

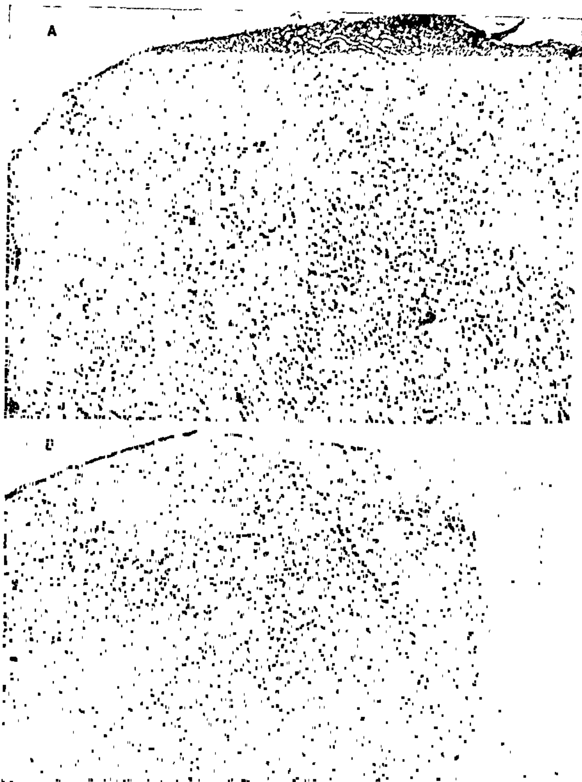



FIG A *Subacute nonspecific pyelonephritis* showing wedges of lymphocytic infiltration alternating with essentially normal parenchyma

FIG B *Lymphocytic leukemic infiltrate* (leukoma) simulating subacute pyelonephritis by virtue of the lymphocytes and the wedge-shape of the infiltrate.




FIG A *Chronic nonspecific pyelonephritis* showing characteristic features of (1) thickened capsule, (2) compact clusters of hyalinized glomeruli, (3) atrophy of tubules, (4) marked thickening of Bowman's capsule in striking contrast to the integrity of the glomerular tufts, and (5) colloid casts, only a few of which are present here. (A.F.I.P. Acc 91842)

FIG B *Pelvis of chronic nonspecific pyelonephritis* with conspicuous lymphocytic infiltrate

## Necrotizing Papillitis

In recent years so much emphasis has been given to a lesion called "necrotizing papillitis" that it has come to be regarded both as a clinical and pathologic entity (Edmundson, Martin, and Evans, Robbins, Mallory, and Kinney). The original description of the condition was made by Friedreich in 1877

### *Pathology*

*Grossly*, the lesion is characterized by whitish or yellowish grey, friable necrotic foci sharply delimited to the pyramids which may be partially or completely replaced by these necrotic areas. One or more pyramids may be involved unilaterally or bilaterally, although the lesions tend to be widespread (plate 191A). *Histologically*, the lesion consists of dense purulent exudate within and between the collecting tubules and extending various distances up into the medulla (plate 191 B, C) The interstitial tissue and the tubular epithelium look ischemically infarcted The periphery of the lesion, corresponding to the gross picture, is abruptly differentiated from the viable parenchyma. The vessels show no unusual change which might be considered responsible for the infarct-like lesion. Renal arteriosclerosis is common because papillitis occurs in more or less elderly diabetics, but certainly many instances of greater arteriosclerosis occur without the necrotizing lesion Significant, primary thromboses are not noted, nor, in fact, are thromboses attributable to the inflammation seen in any appreciable degree A lesion quite like necrotizing papillitis has long ago (1901) been produced experimentally with vinylamin (Levaditi), thalline, orthothalline and anathalline (Rehns). Levaditi's paper is a superb example of the integration of chemical and morphologic investigations.

### *Pathogenesis*

Necrotizing papillitis is by no means a specific lesion of diabetes mellitus Only about two thirds of the cases are found in diabetics, the lesion occurs in about 3 per cent of a sied diabetics. In all instances in diabetics, lesion appears associated with a severe a ascending pyelonephritis; in no ,
struction in the urinary tract ı

cases. Precisely what the pathogenesis of this ischemic type of medullary necrosis is, remains unclear. It has been suggested that acutely increased intrapelvic pressure on the pyramids abetted by pressure of the interstitial purulent exudate on the peritubular capillaries may result in interference with the medullary blood supply. The pathogenesis of the experimental necrotizing papillitis (vinylamine and thalline) is equally nebulous

### *Clinical Picture*

When the lesion is bilateral and involves most of the pyramids, it leads to rapidly progressive and fatal renal insufficiency, after a sudden onset with fever, leukocytosis, pyuria and often hematuria. A similar volume of infarcted renal tissue otherwise distributed might not cause such interference with renal function, but in this entity, the necrosis is strategically situated at the papillae where outflow is jeopardized. Sloughing of whole papillae has been described

*In view of the apparent relationship* of necrotizing papillitis to acute suppurative pyelonephritis, generally of the ascending obstructive type, considerable precautions should be taken when surgical procedures are contemplated on the genito-urinary tract of elderly diabetics, because of their vulnerability to infection In addition to the chemotherapeutic measures, consideration should be given as to whether or not ureters from a diabetic patient should be transplanted to the infective area of the bowel rather than to the skin, despite some of the mechanical advantages to the patient of the former procedure Another advantage of cutaneous transplantation of ureters in a diabetic patient is that glycosuria may be more readily estimated and controlled The problem is of course an individual one but failure to weigh these factors has led to fatalities

## Par Abscess

Paranephric Its from (1) direct
ension of r n, (2) lymphatic
sport of inf or from
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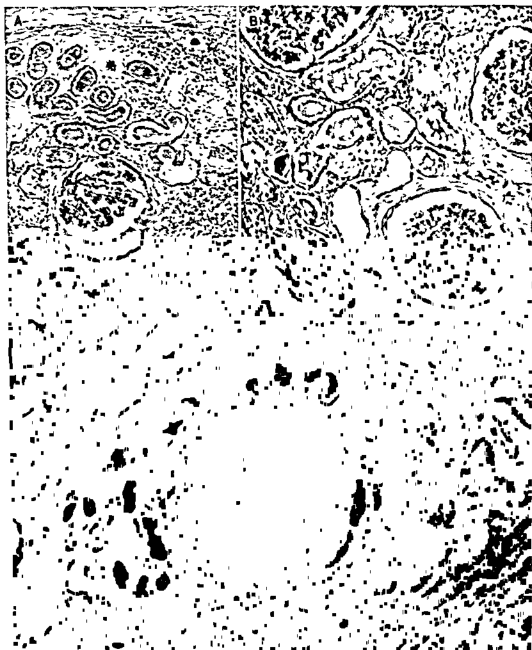



FIG A *Chronic pyelonephritis* with colloid casts, atrophic glomeruli, interstitial lymphocytic inflammation, widened Bowman's space and thickened Bowman's capsule

FIG B *Chronic pyelonephritis* with obvious disparity in degree of fibrosis of Bowman's capsule and the contained malpighian tufts

FIG C *Hyperplastic sclerosis* along with colloid casts, thickening of glomerular capsule, dilatation of Bowman's space, interstitial fibrosis and arteriolar sclerosis




FIG A *Pyelitis and ureteritis cystica*

FIG B. *Pyelitis cystica* with calcification of cystic contents.

FIG C *Pyelitis cystica* The cysts are not the result of dilatation of Brunn's nests but are formed by vesiculation directly within the epithelium



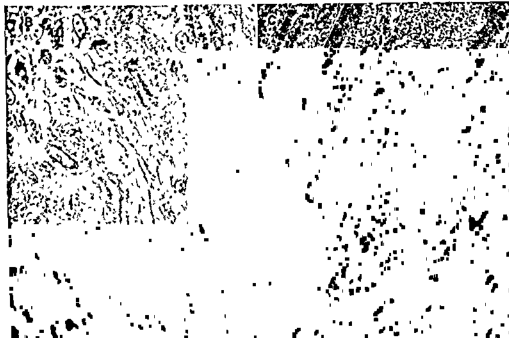




FIG A *Necrotizing papillitis* in a diabetic patient The lesion may involve any or all of the papillae (courtesy Dr. W A D Anderson)

FIG B. *Necrotizing papillitis* showing the infarct-like type of necrosis (nondiabetic)

FIG C *Necrotizing papillitis* with extensive leukocytic infiltration in addition to bland necrosis (diabetic).

common route is from an abscess of the kidney. In any case, the therapy of the local abscess is independent of its pathogenesis

The diagnosis of paranephric abscess is based on local pain, costo-muscular tenderness, irritation and spasm of the psoas muscle with resultant flexion of the hip joint, and systemic signs of infection The pain may be referred to the hip joint and the contraction of the psoas may be taken to indicate a psoas abscess. The paranephric abscess may point in odd locations, such as Scarpa's triangle, above the iliac crest through Petit's triangle, and even through the diaphragm to cause pleural empyema Because the paranephric abscess almost always causes perinephritis, there is abnormal fixation of the kidney in contrast to the opposite side This feature of immobility may be demonstrated with pyelograms The pyelogram may also be distorted by the abscess and may simulate a neoplasm.

## Hydronephrosis

### *Introduction*

Hydronephrosis is one of the most common renal disorders and refers to the dilatation of the renal pelvis and calyces usually with atrophy of the parenchyma The hydronephrosis may be partial or complete, that is, it may not affect all of the calyces "Closed" or "open" hydronephrosis indicates respectively the complete or incomplete blockage of the ureter In "intermittent" hydronephrosis, the nature of the obstruction is such that it is relieved periodically The names "extrarenal" and "intrarenal" hydronephrosis indicate essentially that the dilated pelvis is extra- or intrarenal in location, this distinction serves very little purpose and is not to be confused with the process of "internal" hydronephrosis The term "internal" hydronephrosis is used to designate the acute dilatation of tubules and Bowman's spaces with normal pelvis and calyces, secondary to intraparenchymal obstruction by crystals (sulfa, calcium oxalate) or casts (plates 142B, 192D), or the early phase in some cases of hydronephrosis due to external obstruction.

### *Etiology*

The causes of hydronephrosis are congenital or acquired. The *congenital causes* include (1) atresia of the ureter, (2) torsion, kink, stricture, or valve of the ureter, (3) anomalous artery with resultant compression or angulation of the ureter, (4) urethral stricture, diverticulum, or valve, and (5) functional or neuromuscular hydronephrosis in which autopsies disclose no organic obstruction, and in which paralysis of the ureterovesical sphincter, or possibly ureteral achalasia appears to be at fault

The *acquired form* of hydronephrosis is produced by calculi, tumors of the ureter, extensions from carcinoma of the prostate, bladder, uterus, ovary, rectum, hypertrophy of the prostate, urethral abnormalities, uterine fibroids, retroperitoneal tumors, pregnancy, ureteral strictures, ureteral transplantations, accidental ureteral ligation, trauma to kidney or ureter, nephroptosis in relation to an accessory artery, pelvic inflammatory disease, and cord bladder secondary to spina bifida, tumors, syphilis, myelitis, amyotrophic lateral sclerosis, multiple sclerosis, or a trauma to the spinal cord. As stated, according to Robertson, "almost every pregnant woman suffers from ureterectasis and pyelectasis (hydronephrosis) from about the beginning of the fifth month of pregnancy to a few weeks after delivery" In most instances, the hydronephrosis, if uncomplicated, rapidly subsides after gestation

### *Clinical Picture*

Unilateral hydronephrosis may be clinically silent or its only symptoms may be those of a mass and the effects of compression by the mass The symptoms are essentially those caused by complications. These are pyogenic infection, hemorrhage into the sac, infrequently rupture of the sac, renal insufficiency in the presence of an abnormal contralateral kidney, [illegible] Hyper-

dronephrosis, as a group, than in control groups This is so despite the ability to produce acute hypertension with reduction of renal blood flow in dogs by the ligation of one ureter (Levy et al ) Isolated cases of the relief of hypertension in humans after removal of a hydronephrotic kidney have been reported. As a rule the hypertension with hydronephrosis is associated with other renal diseases, such as benign nephro-

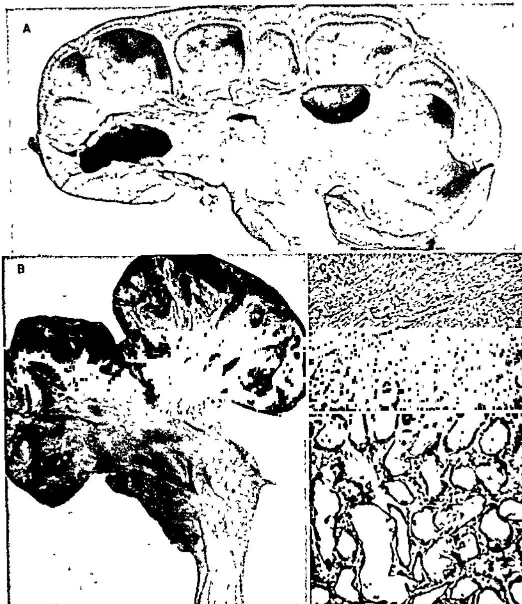



FIG A *Hydronephrotic atrophy* due to constriction at ureteropelvic junction The ureter is of normal diameter The pyramids are naturally reamed out before the cortex because of the direction and application of the hemodynamic vectors (A F I P. Acc 15217)

FIG B *Hydronephrosis with* hydroureter due to obstruction by neoplasm at distal end of ureter.

FIG C *Capsular thickening* and adherence in hydronephrotic atrophy

FIG D. *Acute internal hydronephrosis* secondary to obstruction by crystals of calcium oxalate in ethylene glycol (antifreeze) poisoning

sclerosis, chronic pyelonephritis, and chronic glomerulonephritis.

*Pathology and Pathogenesis of Hydronephrosis*

*Gross appearance*

Statements vary as to the effect of ureteral obstruction on the kidney. The best evidence is that with sudden complete obstruction and resultant *closed* hydronephrosis, the kidneys may undergo atrophy with over-all diminution in size (in rare cases) According to Hinman, such atrophy may follow not only complete hydronephrosis but also partial and intermittent hydronephrosis However, he stresses that this type of atrophy of the kidney is an exceptional occurrence in both man and animals and that, except for these rare instances, the kidney enlarges with hydronephrosis after ureteral obstruction The frequency with which the pancreas and salivary glands shrink after obstruction of their main ducts indicates a response of these organs strikingly different from that of the kidney In the case of all three organs, the abrupt cessation of secretion or glomerular filtration after obstruction would seem to be the simplest and most reasonable explanation for the primary atrophy Urologists disagree, however, and place great importance on the unique role of pyelorenal backflow

The large hydronephrotic sacs follow open or intermittent obstruction with some degree of renal function persisting along with the progressive dilatation Those huge closed hydronephrotic sacs that appear to follow complete occlusion are probably associated early with intermittent or incomplete occlusion In the intermittent hydronephrosis, part of the contents of the sac is discharged from time to time with some relief of symptoms, after which the sac is refilled The fluid in the closed sac is not altogether of constant composition, since some excretion and, perhaps, absorption takes place continually Pyelovenous, tubulolymphatic, pyelolymphatic and interstitial backflow contribute to this interchange, according to Hinman These forms of backflow which are stressed almost exclusively by urologists and roentgenologists, are often suggested by radiographic shadows indicative of urovenous backflow after retrograde pyelograms Some observers attribute the backflow to rupt veins or lymphatics; others, such as Hir point to the analagous resorption of aq humor from the anterior ocular chambe the veins of the sclera without apparent communication

With obstruction, the pelvis dilates A pelvis with a capacity greater than 10 cc stitutes a hydronephrosis In extreme cases sac may be distended to the size of 10 t liters The pressure of the fluid enclosed in renal pelvis gradually obliterates the pyra and compresses the columns of Bertin septa (plate 192A). With further atrophy, cortex is reduced in thickness, and the sur of the kidney becomes bosselated as the lob are reamed out. Eventually the septa are literated and all that remains of the kidney thin fibrous pouch

The normal contralateral kidney underg progressive hypertrophy concurrently with hydronephrotic destruction of the opposite k ney. The explanation of this compensatory h pertrophy is included in the theory of *re counterbalance.* Experimentally, if one kidn of a dog is left intact and the other obstructe no permanent repair follows the removal of th obstruction after 45 days, and very little aft 30 days (Hinman). According to the theory renal counterbalance, the compensatory hype trophy of the intact kidney eliminates th need, so to speak, for the obstructed kidney t repair itself. On the other hand, removal of on kidney with the production of simultaneou closed hydronephrosis of the other, results i fatality in 14 days in most animals If th nephrectomy is delayed a few weeks, however many dogs survive when the hydronephrosis of 21 days duration is relieved. If a gradual "autonephrectomy" is produced by incomplete obstruction of the ureter, the opposite kidney with a completely closed hydronephrosis of 30 to 40 days duration may be so stimulated to repair after removal of the obstruction, as to perform adequate total renal function.

In other words, the degree of repair of a hydronephrotic kidney after contralateral nephrectomy depends on when, in relation to the onset of hydronephrosis, nephrectomy is performed despite the originally equal damage



FIG A *Calculous hydronephrotic atrophy* with hydroureter and ureteral pseudo-valve formation

FIG B *Marked hydronephrotic atrophy* of kidney showing entire remaining width from pelvis to capsule reduced to a thin rim

# 11. Renal Calculi

### *Incidence*

RENAL calculi are present in about 5.4 per cent of all autopsies (Rosenow). However, most of these are instances of small, incidental calculi not productive of clinical symptoms or significant renal damage. In approximately 0.4 per cent of autopsies, the renal calculi are directly responsible for death either because of extensive pyelonephritis with uremia, or as a result of complications after operations for the calculi. Renal stones are infrequent in the early decades, about 1 per cent of cases occur in children under 10 years of age and may be associated with renal rickets. Approximately 50 per cent of cases are in the age group of 30 to 50 years (Randall). In Bell's series, the maximum incidence was between the ages of 50 and 75 years. In most series, there is a predominance of occurrence of calculi in males, the ratio being about 4 to 3 (Bell). The stones were somewhat less common on the right side than the left side in Bell's series and occurred bilaterally in 30 per cent of his cases. The preponderance of their occurrence on one side over the other varies with different series and it appears likely that the difference is not statistically significant. The 30 per cent incidence of bilaterality of stones is higher than the clinical figure of 8 per cent usually quoted, but Bell's data come from autopsies in which small, clinically undetected calculi are discovered. There is a greater likelihood of bilaterality of stones if the calculus in one kidney is branched rather than unbranched.

### *Clinical Picture*

Renal calculi produce attacks of dysuria, hematuria, pyuria, colic with local or radiating pain, and even anuria. The colicky pain occurs when the stones pass down the ureter or are wedged into the ureteral lumen. The attacks come on at irregular intervals varying from days to years. The anuria may be initiated without prior warning of pain. The anuria of the opposite kidney is attributed to reflex suppression of function. "Reflex anuria" is a very real phenomenon, and is reproducible experimentally. The anuria with renal calculi is always a serious complication, and frequently proves fatal in from 4 to 16 days, as with anuria from other causes. The obstructing calculi may be in the pelvis or ureter. Not all renal calculi cause significant obstructive renal damage.

Calculi may lie dormant for many years. Small stones may be passed in the urine periodically. Bell records one patient who passed more than 300 calculi over a period of four years.

The diagnosis of renal calculi may be established by the clinical picture supplemented with data from urinalysis for crystals, calcium (Sulkowitch test) and evidence of infection, by intravenous urography, by retrograde instrumentation, by pyelograms with contrast media and by lateral pyelograms.

### *Causes of Renal Calculi*

Some of the causes of renal lithiasis are: primary and secondary hyperparathyroidism, bone diseases, idiopathic hypercalciuria, chronic stasis with infection in the urinary tract, gout, cystinuria, oxaluria, xanthinuria, phosphaturia, and possibly vitamin A deficiency, and excess of vitamin D, or ertron (Kaufman). The cause of the largest number of cases has been attributed to idiopathic hypercalciuria (Albright and Reifenstein). It is generally believed that hyperparathyroidism accounts for 0.1 to 0.2 per cent of renal stones, although Albright and Reifenstein place the incidence near the high figure of 5 per cent.

With regard to urostasis, it is reported that a factor in the production of renal stones in natives of India is their incredible ability to refrain from micturating for days at a time (Roberts, Begg). Deficiency in vitamin A is responsible for abnormal keratinization of epithelium in a variety of locations, including bronchioles, pancreatic ductules, skin, and the urinary tract. The solitary stones in the urinary bladder in Syrian boys have been attributed to

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### *Histologic Appearance*

Remarkably little or no parenchymal change may be noted in many cases in early *hydronephrosis*, even if the obstruction *is bilateral* and severe enough to *cause uremia and* death. In the minority of cases, the cortical tubules and Bowman's spaces may *show dilatation* Thereafter, there is progressive atrophy of the tubules and glomeruli. The more vulnerable proximal convoluted tubules are the first to show evidence of degeneration, with loss of alkaline phosphatase (Wilmer), atrophy and ultimate replacement by fibrosis. The glomeruli become hyaline patches and the remainder of the tubules becomes isolated in a relatively increased stroma infiltrated with scattered mononuclear cells. The vessels are narrowed by the type of sclerotic intimal *thickening that* accompanies the atrophy of disuse. The capsule is *usually* thickened by fibrous tissue and some torpid perinephritis may coexist (plate 192C). Pyelitis and pyelonephritis are almost always *concomitantly* present as is to be expected from *the nature* of the etiology of hydronephrosis

REFERENCES


BELL, E T Renal Diseases Philadelphia, *Lea and* Febiger, 1946

EDMUNDSON, H A , MARTIN, H E , AND EVANS, N G Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus Arch *Int Med* **79:** 148–175, 1947.

FRIEDREICH, N Ueber Necrose der Nierenpapillen bei Hydronephrose Virchow's Arch f path Anat **69.** 308–312, 1877

HELMHOLZ [illegible] for ba[illegible] ney w[illegible] *Child* **31:** 856–862, 1926

HINMAN, F Principles and Practice of Urology Philadelphia, Saunders, 1935

LEVADITI, C Experimentelle Untersuchungen über die Nekrose der Nierenpapille Arch internat de pharmacodyn et de therap **8:** 45–63, 1901

LEVY, S E , MASON, M F , HARRISON, T R , AND BLALOCK, A Effects of ureteral occlusion on blood flow *and oxygen consumption of* kidneys of unanesthetized dogs Surgery *1:* 238–242, 1937.

LÖHLEIN, M. Über Schrumpfnieren Beitr *z. path.* Anat u z allg Path **63**· 570–632, 1917

LONGCOPE, W T , AND WINKENWERDER, W L · Clinical features of the contracted kidney *due to* pyelonephritis Bull Johns Hopkins Hosp **53.** 255–287, 1933

MALLORY, G K , CRANE, A R , AND EDWARDS, J E · Pathology of acute and of healed experimental pyelonephritis. Arch Path **30:** 330–347, 1940.

REHNS, J D'une nécrose typique de la papille rénale determinée par la tetrahydroquinoléine et certains de ses dérivés. Arch. internat de pharmacodyn et de thérap **8:** 199–202, 1901

ROBBINS, S. L , MALLORY, G K , AND KINNEY, T D Necrotizing renal papillitis, a form of acute pyelonephritis New England J Med **235.** 885–893, 1946

ROBERTSON, H E., Hydronephrosis and Pyelitis (Pyelonephritis) of Pregnancy. Etiology and Pathogenesis Philadelphia, London. Saunders, 1944, p 253–256.

SMITH, G G Late results of ureteroenterostomy Surg , Gynec., & Obst. **85:** 221–227, 1947

STAEMMLER, M , AND DOPHEIDE, W Die pyelonephritische Schrumpfniere Virchow's Arch f path Anat **277:** 713–756, 1930

VOLINI, I F , AND FLAXMAN, N . The effects of nonspecific operations on essential hypertension. J A. M A **112:** 2126–2128, 1939

WEINBERG, T Contralateral adrenal atrophy associated with cortical adrenal neoplasms N Y State J Med **41:** 884–886, 1941

WEISS, S , AND PARKER, F , JR Pyelonephritis its relation to vascular lesions and to arterial hypertension Medicine **18:** 221–315, 1939

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### *Clinical Picture*

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The diagnosis of renal calculi may be established by the clinical picture supplemented with data from urinalysis for crystals, calcium (Sulkowitch test) and evidence of infection, by intravenous urography, by retrograde instrumentation, by pyelograms with contrast media and by *lateral pyelograms.*

### *Causes of Renal Calculi*

Some of the causes of renal lithiasis are: primary and secondary hyperparathyroidism, bone diseases, idiopathic hypercalciuria, chronic stasis with infection in the urinary tract, gout, cystinuria, oxaluria, xanthinuria, phosphaturia, and possibly vitamin A deficiency, and excess of vitamin D, or ertron (Kaufman). The cause of the largest number of cases has been attributed to idiopathic hypercalciuria (Albright and Reifenstein). It is generally believed that hyperparathyroidism accounts for 0.1 to 0.2 per cent of renal stones, although Albright and Reifenstein place the incidence near the high figure of 5 per cent.

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### References


BELL, E T Renal Diseases Philadelphia, Lea and Febiger, 1946

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LÖHLEIN [illegible]
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Clinical features of the contracted kidney due to pyelonephritis Bull Johns Hopkins Hosp. 53: 255-287, 1933

MALLORY, G K, CRANE, A R, AND EDWARDS, J E Pathology of acute and of healed experimental pyelonephritis. Arch Path. 30· 330-347, 1940.

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Calculi may lie dormant for many years. Small stones may be passed in the urine periodically. Bell records one patient who passed more than 300 calculi over a period of four years.

The diagnosis of renal calculi may be established by the clinical picture supplemented with data from urinalysis for crystals, calcium (Sulkowitch test) and evidence of infection, by intravenous urography, by retrograde instrumentation, by pyelograms with contrast media and by lateral pyelograms.

## *Causes of Renal Calculi*

Some of the causes of renal lithiasis are: primary and secondary hyperparathyroidism, bone diseases, idiopathic hypercalcinuria, chronic stasis with infection in the urinary tract, gout, cystinuria, oxaluria, xanthinuria, phosphaturia, and possibly vitamin A deficiency, and excess of vitamin D, or ertron (Kaufman). The cause of the largest number of cases has been attributed to idiopathic hypercalciuria (Albright and Reifenstein). It is generally believed that hyperparathyroidism accounts for 0.1 to 0.2 per cent of renal stones, although Albright and Reifenstein place the incidence near the high figure of 5 per cent.

With regard to urostasis, it is reported that a factor in the production of renal stones in natives of India is their incredible ability to refrain from micturating for days at a time (Roberts, Begg). Deficiency in vitamin A is responsible for abnormal keratinization of epithelium in a variety of locations, including bronchioles, pancreatic ductules, skin, and the urinary tract. The solitary stones in the urinary bladder in Syrian boys have been attributed to

under each condition (Hinman). The factor of renal "stimulation" to repair, created by an adequate or inadequate opposite kidney, embodies a principle well known in the behavior of other organs, as, for example, the contralateral cortical atrophy of the adrenal gland in the presence of a functional cortical carcinoma of the other adrenal (Weinberg) This principle has therapeutic application in evaluation of surgical procedures in unilateral renal disease of humans.

### *Histologic Appearance*

Remarkably little or no parenchymal change may be noted in many cases in early hydronephrosis, even if the obstruction is bilateral and severe enough to cause uremia and death. *In the minority of cases, the cortical tubules* and Bowman's spaces may show dilatation Thereafter, there is progressive atrophy of the tubules and glomeruli The more vulnerable proximal convoluted tubules are the first to show evidence of degeneration, with loss of alkaline phosphatase (Wilmer), atrophy and ultimate replacement by fibrosis The glomeruli become hyaline patches and the remainder of the tubules becomes isolated in a relatively increased stroma infiltrated with scattered mononuclear cells. The vessels are narrowed by the type of sclerotic intimal thickening that accompanies the atrophy of disuse. The capsule is usually thickened by fibrous tissue and some torpid perinephritis may coexist (plate 192C). Pyelitis and pyelonephritis are almost always concomitantly present as is to be expected from *the nature of the etiology of hydronephrosis.*

## REFERENCES


BELL, E T Renal Diseases Philadelphia, Lea and Febiger, 1946

EDMUNDSON, H A, MARTIN, H E, AND EVANS, N G Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus Arch Int Med 79: 148–175, 1947.

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# 11. Renal Calculi

*Incidence*

RENAL calculi are present in about 5 4 per cent of all autopsies (Rosenow) However, most of these are instances of small, incidental calculi not productive of clinical symptoms or significant renal damage In approximately 0 4 per cent of autopsies, the renal calculi are directly responsible for death either because of extensive pyelonephritis with uremia, or as a result of complications after operations for the calculi. Renal stones are infrequent in the early decades, about 1 per cent of cases occur in children under 10 years of age and may be associated with renal rickets Approximately 50 per cent of cases are in the age group of 30 to 50 years (Randall) In Bell's series, the maximum incidence was between the ages of 50 and 75 years In most series, there is a predominance of occurrence of calculi in males, the ratio being about 4 to 3 (Bell) The stones were somewhat less common on the right side than the left side in Bell's series and occurred bilaterally in 30 per cent of his cases The preponderance of their occurrence on one side over the other varies with different series and it appears likely that the difference is not statistically significant The 30 per cent incidence of bilaterality of stones is higher than the clinical figure of 8 per cent usually quoted, but Bell's data come from autopsies in which small, clinically undetected calculi are discovered There is a greater likelihood of bilaterality of stones if the calculus in one kidney is branched rather than unbranched

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cidence near the high figure of 5 per cen

With regard to urostasis, it is report
a factor in the production of renal st
natives of India is their incredible ab
refrain from micturating for days at
(Roberts, Begg). Deficiency in vitamin
sponsible for abnormal keratinization
thelium in a variety of locations, in
bronchioles, pancreatic ductules, skin, a
urinary tract. The solitary stones in the
bladder in Syrian boys have been attrib

deficiency in this vitamin (Brown and Brown) It is this type of association that has prompted the therapeutic and prophylactic use of vitamin A in patients with calculi The results have not been encouraging

### *Composition of Renal Calculi*

Calculi are composed chiefly of carbonates, amorphous and crystalline phosphates, oxalates, uric acid and urates Infrequently calculi are made up of xanthine, cystine, foreign bodies, fibrin, bacterial masses, and rarely indigo, cholesterin and fatty urostealiths

The so-called primary stones tend to form in faintly acid or neutral urine These include stones of uric acid, urates, oxalates, xanthine and cystine The "secondary" calculi are precipitated in alkaline urines; these are calculi of ammonium magnesium phosphate and amorphous calcium carbonate and phosphate

Most large calculi are mixed, they are usually constructed of a nucleus of one chemical, often uric acid or urates, with outer coats of carbonates and phosphates (plate 195) Actually, a stone of pure chemical composition does not occur although those stones containing 90 per cent of one substance are loosely called pure Data on the chemical make-up of the nucleus of a calculus are of more value with regard to the determination of the etiology than information about its peripheral composition The nature of calculi differs in various parts of the world, principally because of diet For example, oxalate stones are especially common among the vegetarian Japanese (Hinman)

### *Methods of Analysis of Calculi*

There is a growing impression that chemical analysis of renal calculi offers no significantly [illegible] r [illegible] curacy of data from routine chemical analysis of calculi

Some of the basic reasons for the gross defects of chemical analysis of stones are (1) the invalidating interference with the standard reactions by organic substances of unknown composition, (2) the technical barriers against the chemical resolution of complex mixtures commonly found in calculi, (3) the quantitative limitations of chemical study of very small calculi, and (4) the confusion regarding the exact nature of the reactions in the qualitative chemical tests (Prien and Frondel)

To eliminate these sources of error, Jensen and later Prien and Frondel have borrowed a technique from minerology which, with a polarizing petrographic microscope, permits an analysis of calculi by virtue of characteristic optical properties of crystalline substances. This method has been supplemented with the x-ray diffraction procedure in which finely powdered calculous material is irradiated by a beam of monochromatic x-rays, the rays diffracted from the planes of the crystals are recorded in varying intensity and spacing on a photographic film Inasmuch as no two compounds have identical crystalline structures, their x-ray diffraction patterns are as individualistic as finger prints The disadvantages of this method are the expense of the apparatus and the complexities of the subject matter These are practical disadvantages of consequence and currently limit the use to specialized investigative work (Prien and Frondel). The diffraction patterns of crystalline substances found in urinary calculi are illustrated in plate 196

It is of interest that renal calculi which have already formed may be made radioactive. Benjamin and his associates demonstrated radioactivity in phosphate calculi in the renal pelvis after administering $P^{32}$ orally.

### *Morphogenesis of Renal Calculi*

The most favored hypothesis of the morphogenesis of calculi is that suggested by Randall. In effect, he believes that calcification in the region of the renal papillae (Randall's plaques) serves as a nidus for the subsequent accretion of calcareous material (plate 204A). The calcified nidus eventually separates itself from the papilla and lies free in the calyx or pelvis to accrue further material, possibly after the manner of formation of stones in a focus of cholesterosis in the gall bladder, or of pearls in an oyster. The observation of small calculi still attached to Randall's calcific plaques at the apex of the papillae is evidence in favor of this mode of origin of at least some of the calculi.










FIG A *Portion of staghorn calculus* in kidney with hydronephrosis and chronic pyelonephritis

FIG B *Calculous pyelonephritis*

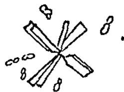
FIG C *Roentgenogram of staghorn renal calculus* (A F I P )

PLATE 195

## CRYSTALS OF RENAL CALCULI



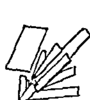
Triple and Amorphous Phosphates



Calcium Phosphate and Dumb-Bell Calcium Sulfate

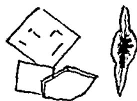


Ammonium Biurate



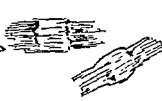
Sodium Acid Urate

## URIC ACID CRYSTALS









Calcium Oxalate

Cystine

Leucine Spheres and Tyrosine Needles



Cholesterol



Calcium Sulfate



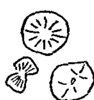
Hippuric Acid



Fatty Acids



Sulfapyridine



Sulfathiazole



Sulfadiazine

Monetite
Calcium Acid Phosphate

Oxamide
Diamide of Oxalic Acid

Sod. Acid Urate

Struvite
Magnesium Ammonium Phosphate Hexahydrate

Uric Acid

Weddellite
Calcium Oxalate Dihydrate

Whewellite
Calcium Oxalate Monhydrate

Whitlockite
Tricalcium Phosphate

Xanthine

X *ray diffraction patterns* of various renal calculi Each pattern is characteristic of the individual chemical composition of the stones (Courtesy of Drs E L Prien and C Frondel J Urol 57 949-991, 1947)

It is doubtful if metastatic calcification of the distal convoluted tubules of itself leads to pelvic calculi by extrusion of the small foci Only when the parenchymal nephrocalcinosis extends to the collecting tubules in the papillae, does it probably contribute to the formation of calyceal and pelvic calculi Moreover, as Albright and Reifenstein point out, hyperparathyroidism may lead to the formation of pelvic calculi, as it often does, without any appreciable calcification of the distal convoluted tubules, and vice versa.

Undoubtedly, another less overtly mechanical factor is responsible for the formation of renal calculi, namely, the physico-chemical situation occurring when the urine is supersaturated with crystalloids The crystalloids are held in a state of dispersion by adsorption to protective colloids. With supersaturation of the urine by excessive excretion of crystalloids, however, the normal colloidal mechanism fails to maintain solution and there is precipitation or gelling of the urinary colloids which form the calcular framework. The role in the formation of calculi played by necrobiotic debris resulting from infections and the keratinous material from epidermalization of the pelvic mucosa is not clear although generally assumed to be of importance.

### *Complications of Renal Calculi*

The complications of renal calculi are (1) pyelitis, (2) pyelonephritis, (3) hydronephrosis, (4) anuria, (5) spontaneous rupture of the kidney, (6) renal lipomatosis, and (7) carcinoma of the renal pelvis

Some calculi—even the large staghorn stones—may produce simple chronic pyelitis without involvement of the renal parenchyma However, chronic pyelonephritis with hydronephrosis is the common result of persistent renal calculosis or of renal calculi that have descended to the ureter Instead of hydronephrotic obstruction and dilatation, the kidney may atrophy with a progressive increase of pelvic fat and perirenal fat referred to as lipomatosis (plate 278C). The deposition of fat may be considerable and may clinically simulate a renal neoplasm. Instances of kidneys with "calculous lipomatosis" are reported in which the kidneys weighed over 1000 Gm. (Bell). In one series of 33 cases of renal lipomatosis, 26 were associated with calculi.

The association of carcinomas of the renal pelvis with calculi as in the case of the urinary bladder, appears more than coincidental The calculi and associated infection tend to provoke a leukoplakia or dyskeratotic squamous cell metaplasia of the epithelium which, in the urinary tract, has a greater tendency to neoplastic change than does the normal epithelium (plates 310, 311). Rarely, the stones are associated with mucus-producing adenocarcinomas (plate 315).

### *Treatment of Renal Calculi*

In most cases, obstructive ureteropelvic calculi, which produce symptoms, evidence of destruction of renal parenchyma, stasis or infection, should be removed operatively by nephrotomy, pyelotomy, or hemi- or total nephrectomy. It is true that some stones, formed in either alkaline or acid urine may be completely dissolved by appropriate dietary means, supplemented with vitamins A and D However, the results are inconstant (Higgins) and should perhaps be reserved for calyceal calculi. The remarkable effect of dietary therapy has been to reduce the rate of frequency of recurrence of renal calculi following operative removal from 16 9 per cent to 2 9 per cent (Higgins). The recurrent failures on the dietary regime occur principally in those patients in whom the urinary pH resists control because of the presence of urea-splitting bacteria in the pelvis. Good results in the attempt to dissolve renal calculi have been obtained by Suby and Albright with the retrograde instillation of citrate solutions at a pH of approximately 4 5, made less irritating with the addition of magnesium oxide. This method was found practical for calculi composed of calcium phosphate, calcium carbonate and magnesium ammonium phosphate Hyaluronidase has recently been tried with indifferent success although it has been suggested by Keyser and his associates that certain other enzymes, particularly urease, give promise of beneficial effects when used in conjunction with the citrate solutions. The aim of the enzymatic therapy is to dissolve the organic matrix which




FIGS. A, B AND C. *Calcification of collecting tubules* at apex of pyramid in association with pelvic calcinosis secondary to hyperparathyroidism. In figures B and C it is noted that the basement membranes of the tubules and the adjacent stroma are encrusted with calcium. This degree of calcification at this strategic outlet for the urinary flow may lead to serious renal dysfunction.




FIG A *Uric acid microcalculi*, collecting tubules and epithelium of a pyramid from a case of gout The usual giant cell reaction is absent (Compare plate 153)

FIG B *Parenchymal nephrocalcinosis* ("metastatic calcification") This same picture is produced by alkalosis, hyperparathyroidism, and extensive metastasis to bones (above) The black masses of calcium are in the lumens and epithelium of the distal convoluted tubules The calcification may be as widespread as illustrated here without detectable interference with renal function

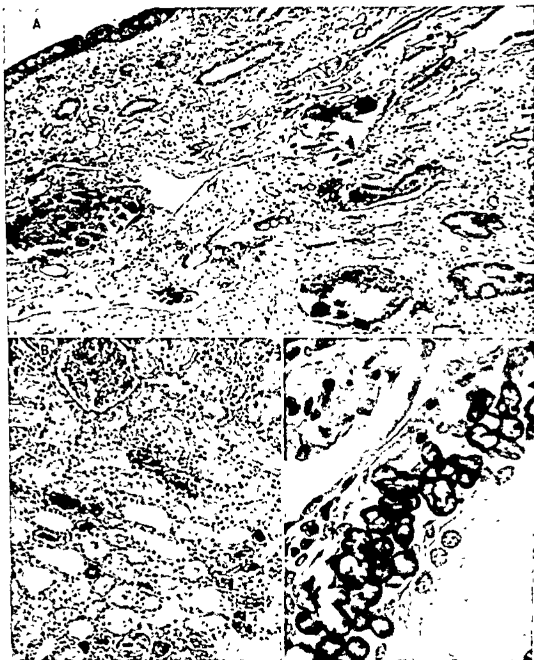



FIG. A. *Calcification of tubular epithelium* and calcium casts in the lumens of collecting tubules as a result of severe alkalosis.

FIG. B. *Calcification of epithelium of distal convoluted tubules* in alkalosis. The renal function was normal. The proximal tubules are altogether spared in contrast to the effect of mercury bichloride.

FIG. C. *Encrustation of epithelial cells* in distal convoluted tubules in alkalosis. The calcified cells are sloughed and coalesce into calcium casts.

resists the solvents useful for crystalline components. Much of the infection associated with renal calculi can now be controlled with antibiotics. Adjustment of metabolic deficiencies, including correction of excessive calciuria and the use of abundant fluids are therapeutic adjuvants.

## Parenchymal Nephrocalcinosis

### *Introduction*

Alkalosis following vomiting or excessive ingestion of alkali, or "metastatic" calcification as a result of hyperparathyroidism, severe osteoporosis from trauma, prolonged immobilization, osteomyelitis, lytic osseous metastases, as from breast cancers or lymphomas, all lead to a qualitatively similar histologic picture in the parenchyma of the kidney. This lesion may be termed "parenchymal nephrocalcinosis" in contradistinction to grossly evident calculi in the renal pelvis. The calcification may occur in a very short time, alkalosis may produce it in several days. There is not necessarily a direct correlation between the extent of the osseous metastases and the degree of renal calcification. Undoubtedly the rapidity of the release of the calcium is a major factor in its disposition by the kidneys. It has been suggested that testosterone commonly produces renal calcification. In the cases at our disposal in which renal calcification has occurred with testosterone therapy, the renal calcification could be accounted for by the osseous metastases from the mammary carcinomas that were being treated.

### *Histologic Appearance*

With the rarest exception, the tubular change in metastatic calcification or alkalosis is clearly limited to the distal convoluted segments. The granules of calcium are deposited directly within the nuclei particularly (plate 199C), but extend also to the cytoplasm of the epithelial cells of the distal tubules (plate 199B). The nuclei are often sharply outlined by the calcific rim. Cellular debris is desquamated into the tubular lumens as calcareous casts.

The calcification is a bland process generally provoking no noteworthy inflammatory reaction. Occasional exceptions occur, however, in which mild leukocytic and epithelial response takes place in the form of regeneration or syncytial fusion so as to simulate a foreign body giant cell (plate 151D). This latter formation in association with calcification resembles the tubular picture of multiple myeloma from which it may be easily distinguished by the absence of typical proteid casts of myeloma in other tubules and the presence of torpid calcification of individual epithelial cells in others. If the tubular epithelial necrosis in alkalosis is marked, it is likely that basic contributory complications, such as shock and dehydration are associated with the alkalosis and may not be given proper weight in the final evaluation. This kind of complication following excessive vomiting appears to have occurred in a case reported as "lower nephron nephrosis" due merely to alkalosis (McLetchie).

As a rule, as stated, the calcium is localized to the distal convoluted tubules and is therefore usually confined to the cortex (plate 198B). In this situation, parenchymal nephrocalcinosis rarely interferes with renal function to any significant degree. However, in the literature, partial to complete renal dysfunction has been attributed to such nephrocalcinosis, despite evidence to the contrary in the form of normal urea clearance tests (Kirsner and Knowlton). This fact is especially pertinent in the exaggerated role attributed to the even lesser degree of histologic tubular damage seen in some cases of hemoglobinuric nephrosis. In exceptional cases, however, the calcification which is in the region of the collecting tubules of the papillae produces partial to complete occlusion of their lumens, destruction of epithelium, and considerable renal insufficiency. The tendency to attribute renal insufficiency merely to the calcification is provoked by the sheer *conspicuousness* of the change and is as unjustified as it would be in the case of extreme hemosiderosis (plate 124B). Finally, no morphogenetic relation of parenchymal nephrocalcinosis, exclusive of calyceal calcification, to gross, pelvic calculi has been demonstrated.

In exceedingly rare cases in which massive amounts of calcium are liberated to the blood stream, the basement membranes of glomerular capillaries, Bowman's capsules and the walls of arcuate, subarcuate, and interlobular arteries

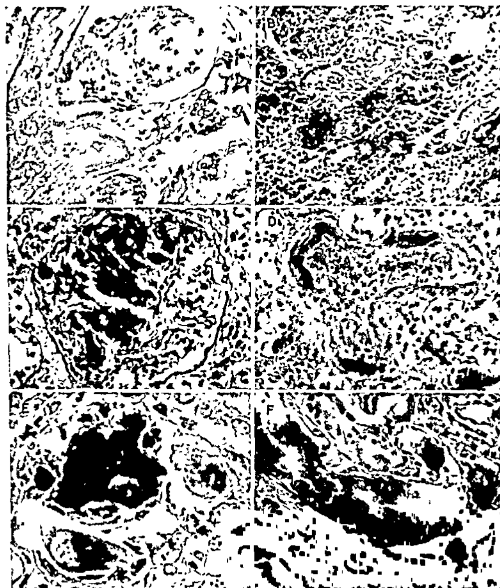



FIG A *Mammary carcinoma*, metastatic to vertebrae, leading to renal calcification as shown in figure B

FIG C *Glomerular calcification* of capillary basement membrane in hyperparathyroidism

FIG E *Metastatic calcification* of a tubular cast of kidney in a case of multiple myeloma

FIG B *Calcification* of epithelium of distal convoluted tubules from the case of mammary carcinoma illustrated in figure A

FIG D *Metastatic calcification* in the wall of interlobular artery in hyperparathyroidism

FIG F *Calcification of necrotic tubular epithelium* due to sulfonamide toxicity



FIG A. *Two foci of ossification* (arrows) in cysts in case of chronic nonspecific pyelonephritis

FIG C *Ossification* of apex of pyramid in hydronephrosis.

FIG B. *Ossification of tubular casts* from a case of multiple myeloma

FIG D *Ossification* of pelvis in hydronephrosis In each of the above cases, the ossification is of a metaplastic rather than dysembryogenic nature

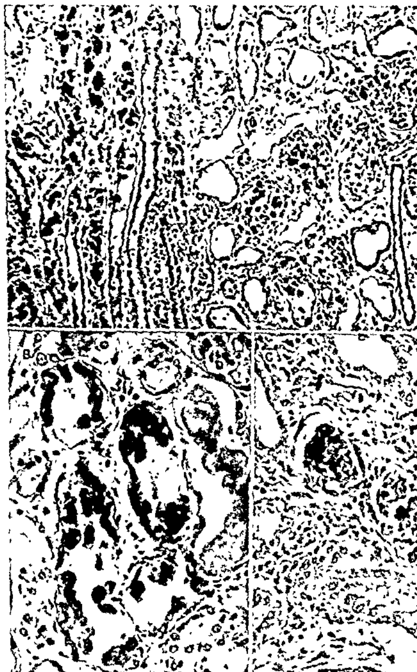



FIG. A. *Mercury bichloride nephrosis with extensive calcification confined to t[illegible] thin distal tubules*

may all become more or less calcified In this circumstance, calcification of the pulmonary alveolar septa, and of the gastric mucosa, and even of the hepatic parenchymal cells may be anticipated The basement membranes of the collecting tubules and adjacent interstitium are not infrequently calcified (plate 197).

### *Differential Diagnosis*

The practical differential histologic diagnosis of parenchymal nephrocalcinosis (alkalotic or metastatic calcification) includes hyperparathyroidism (plate 200C, D), mercurial nephrosis (plate 202A), sulfonamide nephrosis (plate 202C), metastatic carcinoma to bones (plate 200A, B), myeloma nephrosis (plate 200E), and rare forms of acute diffuse glomerulonephritis with tubular calcification (plate 202B) The calcification in mercurial nephrosis and in acute glomerulonephritis is localized to necrotic epithelium of the *proximal* rather than the distal tubules. The calcification of sulfonamide nephrosis, metastatic osseous carcinomatosis, and myeloma nephrosis is really the equivalent of alkalotic or metastatic calcification superimposed on other changes, described elsewhere, which are produced in these conditions The particularly revealing feature of alkalotic or metastatic calcification is the tendency for the exquisite outlining of the epithelial nuclei by the basophilic calcium Finally, as previously indicated, alkalosis may occur with shock or other associated circumstances which, rather than alkalosis, may be responsible for the prominent epithelial regeneration and renal dysfunction It is obviously unwarranted, in such instances, to attribute the tubular change and renal dysfunction solely to alkalosis.

### Hyperparathyroidism and the Kidney

Hyperparathyroidism may be (1) primary or (2) secondary Primary hyperparathyroidism is caused either by hyperplasia, or adenoma, or, in rare instances, by carcinoma of the parathyroid glands. Secondary hyperparathyroidism results from hyperplasia of the parathyroid glands provoked by renal insufficiency It follows that a neoplasm of the parathyroid gland producing a state of primary hyperparathyroidism may be responsible for the cycle of nephrolithiasis, pyelonephritis, renal insufficiency and resultant hyperplasia of the other parathyroids or secondary hyperparathyroidism.

In the primary or secondary hyperparathyroidism, there is hypercalcemia with hypercalciuria, hypophosphatemia (with normal urea clearance), increased serum alkaline phosphatase in the presence of bone lesions, with poly*dipsia, polyuria, nocturia,* often with increased excretion of chloride and base. Hypercalcemia itself may produce symptoms of muscle weakness, decreased excitability, constipation and vomiting, anorexia and skeletal pain

The stimulus to parathyroid hyperplasia in renal insufficiency was formerly thought to be the hypocalcemia caused by retention of phosphates, in accordance with the law of the products of solubility The current thought is that the regulator of the hyperplasia is the hyperphosphatemia; the injection of phosphates in animals leads to parathyroid hyperplasia (Drake et al ).

In a very high percentage of cases (52, or 81 per cent, of 64 cases of Albright and Reifenstein) hyperparathyroidism is associated with *parenchymal nephrocalcinosis or pelvic* lithiasis often in association with osteitis fibrosa cystica or generalisata and occasionally with osteosclerosis (Ginzler and Jaffe). However, hyperparathyroidism may occur with or without renal calcinosis, and with or without bone disease Occasionally, hyperparathyroidism, with hypercalcemia and nephrocalcinosis, may be simulated by lytic metastatic carcinomatosis—particularly rapidly developing metastases—to bones such as may occur with mammary carcinomas. In the case illustrated in plate 200A, B, the level of serum calcium was 22 4 mg No significant renal insufficiency was present, incidentally, despite the widespread renal calcification.

### *Histologic Changes in Parathyroids in Hyperparathyroidism*

The histologic features of the parathyroid of primary hyperplasia, secondary hyperplasia and adenoma are not quite as sharply distinctive as treatises on the subject would indicate.







FIG. A. *Parathyroid adenoma.* Usually the residual cap of the original parathyroid gland may be observed. All patients with renal calculi should be investigated for hyperparathyroidism.

FIG. B. *Parathyroid adenoma* (from tumor illustrated in figure A) composed of broad sheets of water clear cells with scattered acidophilic cells.

FIG. C. *Parathyroid adenoma* (from tumor illustrated in figures A and B) composed of cords of acidophilic cells and conspicuous stroma.

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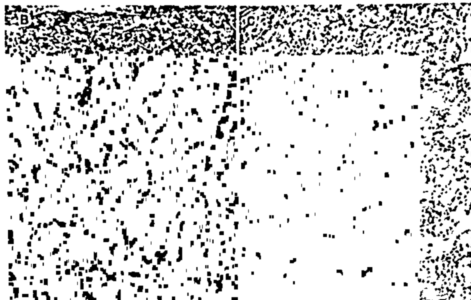



FIG A *Parathyroid adenoma* Usually the residual cap of the original parathyroid gland may be observed All patients with renal calculi should be investigated for hyperparathyroidism

FIG B *Parathyroid adenoma* (from tumor illustrated in figure A) composed of broad sheets of water-clear cells with scattered acidophilic cells

FIG C *Parathyroid adenoma* (from tumor illustrated in figures A and B) composed of cords of acidophilic cells and conspicuous stroma




(Legends on facing page)

As a rule, however, the following details are fairly characteristic:

*Adenoma*

1. Most commonly, one gland, but occasionally only a portion of a gland or multiple glands are involved (in about 6 per cent of cases) (Norris).
2. The adenoma is usually composed not only of the chief (principal) cell but modified chief cells, that is, water-clear ("wasserhelle") cells, oxyphil cells or a mixture of cell types may occur, as in the case illustrated in plate 203.
3. The adenomatous cell is generally larger than normal, often with giant and multiple nuclei.
4. Fat is scanty and the fibrous stroma is irregular in distribution
5. In Norris' 317 cases collected from the literature, there was a female predominance of 3 to 1 when single adenomas were present and 4 to 1, when multiple

*Carcinoma*

Carcinomas of the parathyroid gland are most uncommon and functioning carcinomas are extremely rare, but do occur (Black and Ackerman).

*Primary hyperplasia*

Primary or idiopathic hyperplasia of the parathyroid glands is also a very infrequent finding All of the glands are likely to be enlarged, greyish white, soft, and poorly delimited The hyperplastic cells are the water-clear cells and they tend to be enormously hypertrophied to from 10 to 40 microns in diameter An alveolar pattern is common and actual microcysts may occur

*Secondary hyperplasia*

1. The parathyroids in secondary hyperplasia, as a rule, are creamy grey rather than brown, smaller, firmer and more variable than the adenoma, carcinoma or the parathyroid gland of primary hyperplasia Usually each of the glands is involved
2. *The cell usually involved is the dark chief* cell and is usually of normal size, without nuclear alteration
3. There is an absence or diminution of interstitial fat
4. The proportion of oxyphil cells is higher than would be expected for the age of the patient
5. The glycogen content of the cells is somewhat greater than that of the cells of adenomas or of primary hyperplasias
6. The normal columns of two to three cells tend to be broadened
7. The pattern of cords may be focally altered to form compact areas, acini and papillary areas (Castleman and Mallory).

REFERENCES


ALBRIGHT, F, AND REIFENSTEIN, E C, JR The Parathyroid Glands and Metabolic Bone Disease Baltimore, Williams & Wilkins, 1948

ANDERSON, W A D Hyperparathyroidism and renal disease Arch Path 27: 753-778, 1939

—— Renal calcification in infancy and childhood J Ped 14: 375-381, 1939

—— Renal calcification in adults J Urol 44 29 34, 1940

BEGG, QUOTED BY KEYSER, L D Urinary lithiasis its cause and prevention, evaluation of contributions to our knowledge during past decade South M J 25 1031-1040, 1932

BELL, E T Renal Diseases Philadelphia, Lea and *Febiger*, 1946

BENJAMIN, J A, NEUMAN, W F, THOMPSON, H E, AND WATERHOUSE, C Radioactive phosphorus ($P^{32}$) used to study phosphate exchange between urine in the renal pelvis and renal calculi containing phosphate Science 111. 498-499, 1950


FIG A *High magnification of calculus of calcium phosphate* in hyperparathyroidism The laminated accretions appear to have been deposited on a Randall's plaque (Courtesy of Dr W A D Anderson, *Pathology*, C V Mosby, and J Urol *44* 29, 1940)

FIG. B *Parenchymal nephrocalcinosis* of kidney in primary hyperparathyroidism, caused by a parathyroid adenoma (Courtesy of Dr W A D. Anderson, *Pathology*, C V Mosby, 1948)

FIG C. *Common tubular microcyst* with calcified crystals and amorphous granules of calcium Such calcified cysts are fairly common, without any relationship to hyperparathyroidism They may be grossly visible as minute yellow flecks

BLACK, B K, AND ACKERMAN, L V. Tumors of the parathyroid, report of 23 cases Cancer 3: 415–444, 1950

BROWN, R K, AND BROWN, E C Urinary stones a study of their etiology in small children in Syria. Surgery 9: 415–424, 1941.

CASTLEMAN, B, AND MALLORY, T. B. Parathyroid hyperplasia in chronic renal insufficiency Am J Path 13. 553-574, 1937

COUNCILL, W A, AND COUNCILL, W. A, JR: Spontaneous rupture of the renal parenchyma associated with renal lithiasis J Urol 63: 441–445, 1950

DRAKE, T G, ALBRIGHT, F, AND CASTLEMAN, B Parathyroid hyperplasia in rabbits produced by parenteral phosphate administration. J Clin. Invest 16: 203-206, 1937

GINZLER, A M, AND JAFFE, H L Osseous findings in chronic renal insufficiency in adults Am J Path 17: 293-302, 1941

GRIFFEN, M, OSTERBERG, A E, AND BRAASCH W F Blood calcium, phosphorus and phosphatase in urinary lithiasis, parathyroid disease as etiologic factor J A M A 111: 683–685, 1938

HERBERT, F K, MILLER, H G, AND RICHARDSON, G O Chronic *renal disease, secondary parathyroid hyperplasia*, decalcification of bone and metastatic calcification J Path and Bact 53: 161–182, 1941

HIGGINS, C C. Etiology and management of renal lithiasis J Urol, 62. 403–409, 1949

—— Panel discussion Urinary tract disorders Cleveland Clinic Quart 17: 175–176, 1950

HINMAN, F The Principles and Practice of Urology Philadelphia, Saunders, 1935

JENSEN, A T On concrements from the urinary tract II Acta chir Scandinav 84: 207–223, 1940

KAUFMAN, P, BECK, R D, AND WISEMAN, R D Vitamin D ("Ertron") therapy in arthritis Treatment followed by massive metastatic calcification, renal damage and death. J A M. A 688–690, 1947.

KEYSER, L D., SCHERER, P. C, AND CLOFFEY, L Studies in the dissolution of urinary calculi perimental and clinical aspects J. Urol 59: 841, 1948

KIRSNER, J. B, AND KNOWLTON, K Acid-base ance, renal function, and gastric secretion du hypochloremia in the dog J. Clin Invest 303-312, 1941.

MCLETCHIE, N. G B: Renal lesions in case of cessive vomiting J Path. and Bact 55. 17 1943

MEYER, K A, AND RAGINS, A B: Carcinoma of parathyroid gland. Surgery 14: 282, 295, 1943

NORRIS, E H. Collective review, parathyroid noma, study of 322 cases Int Abst Surg 84 41, 1947.

PRIEN, E L., AND FRONDEL, C: Studies in urolith sis, composition of urinary calculi J. Urol 949–994, 1947.

RANDALL, A Etiology of primary renal calcul Internat Abstr. Surg 71: 209–210, 1940, in Su Gynec & Obst Sept 1940

—— Papillary pathology as precursor of prim renal calculus J Urol 44: 580–589, 1940

ROBERTS, A E Vesical calculus in India, its dist bution and a theory of its cause. Indian Lan 7: 109–115, 1896

ROSENOW, E C, JR Renal calculi; study of pap lary calcification J Urol 44: 19–28, 1940

SUBY, H I, AND ALBRIGHT, F · Dissolution of ph phatic urinary calculi by the retrograde int duction of a citrate solution containing ma nesium New England J Med 228· 81–91, 194

WOLF, I J Safety of large doses of vitamin D in t prevention and treatment of rickets in infanc J Pediat 22: 707–717, 1943.

# 12. Renal Rickets

## *Introduction*

DISTURBANCES in ossification come not only from dietary deficiency, inadequate sunshine, and loss of calcium and vitamin D in celiac and possibly hepatic diseases, but also as a result of diseases of the kidney. Children with chronic renal disease are inclined to be retarded in growth and to manifest osteodystrophic changes that are generally termed "renal rickets." Renal rickets (renal dwarfism, osteonephropathy, renal infantilism) is then a clinical syndrome characterized by dwarfism, skeletal deformities of rickets that are refractory to antirachitic therapy (e.g., rachitic rosary, bossing of skull, bowing of legs), occasional retardation of sexual development, distinctive biochemical changes in the blood and urine, and renal disease of various kinds. As just indicated, the renal lesion associated with renal rickets is not a specific one, but includes any disorder of the kidney in childhood sufficiently severe to interfere with renal function. In this category are included hypoplasia, congenital polycystic kidneys, chronic glomerulonephritis, chronic pyelonephritis and hydronephrosis. In addition, renal rickets occurs with ill-defined renal lesions as in some instances of the de Toni-Fanconi syndrome, about which more will be mentioned.

The biochemical changes are essentially a disturbance in the relationship of calcium and phosphorus. In general, the changes include hypocalcemia, hyperphosphatemia, hypercalciuria, acidosis and azotemia. The bone lesions, in addition to those of dwarfism and rickets, are those of osteitis fibrosa cystica. These latter changes are caused by hyperparathyroidism secondary to the renal insufficiency. Calcium is thereby depleted from bones, and additional increments of calcium are lost by the combination of ingested calcium with phosphates excreted by the intestine to form unabsorbable calcium salts. In some instances, the renal background of the bony changes may be latent so that operations have been performed on bones under the mistaken impression that the osseous lesions were primary. The disturbance in renal metabolism may be so profound as a result of the renal disorder that an astonishing premature calcification of large arteries may occur.

## *Variants of Renal Rickets*

The biochemical changes of renal rickets are not altogether constant and naturally there has been some attempt at further segregation of the cases on the basis of biochemical data. For example, Albright and Reifenstein emphasize the distinction between "renal rickets" and renal acidosis. They attribute the latter to "tubular insufficiency without glomerular insufficiency" although they admit the pathologic findings in the kidney are obscure. There is at least one variant of renal rickets, however, in which the biochemical features are sufficiently distinctive to warrant separate consideration at this time. This variant is known as the de Toni-Fanconi syndrome.

## *de Toni-Fanconi Syndrome*

The de Toni-Fanconi syndrome is a form of renal rickets with certain biochemical variations (hypophosphatemia, glycosuria, aminoaciduria). The syndrome occurs principally in consanguine children, but cases in adults have been recorded (McCune et al.). The bony lesions are those of rickets or osteomalacia in the adult, and of rickets, dwarfism and osteitis fibrosa prior to puberty. The biochemical changes are hypophosphatemia with normal levels of serum calcium, hyperchloremia, normoazotemia, hypophosphaturia, albuminuria, hyperaminoaciduria, particularly cystinuria,

with a normal blood level of amino acids, renal glycosuria, a lowering of blood bicarbonate, usually alkaline urine, and an excess of other organic acids in the urine including lactic acid and beta-hydroxybutyric acid. With the terminating renal insufficiency, hyperphosphatemia with low levels of calcium is likely to occur.

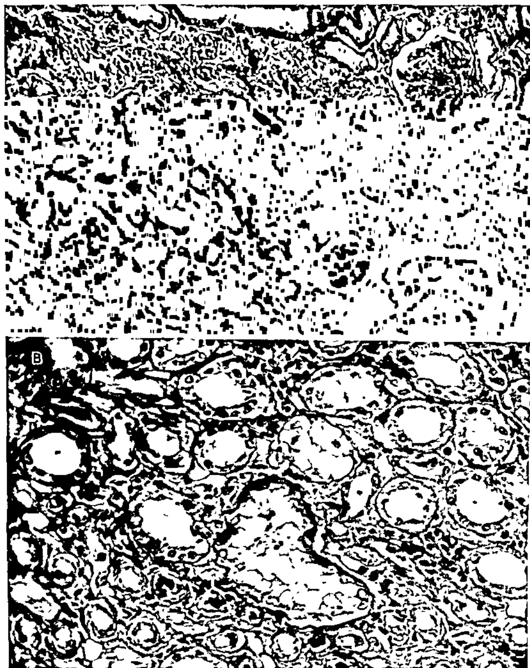
*Pathogenesis*

The explanations of this complicated physiologic derangement have been varied and at the present time, none is entirely satisfactory. It is not clear if the biochemical changes are the result or the cause of the renal changes The possibility that the aminoaciduria itself produces renal damage is strengthened by the evidence of the deleterious effects on the kidney following the experimental administration not only of cystine (Cox et al ), but of other amino acids, including serine, lysine, arginine, histidine, aspartic acid and tryptophane The other explanation offered is that the hyperaminoaciduria, glycosuria, and hyperphosphaturia are attributable to low renal thresholds, inasmuch as the blood levels of these substances are not elevated Hottinger suggests that in some instances the reducing substance in the urine may be *cysteine* and may be mistaken for glucose Fanconi believes that the aminoaciduria is caused by a faulty renal oxidative deamination McCune suggests as a further possibility that the hyperphosphaturia may be the result of hyperparathyroidism.

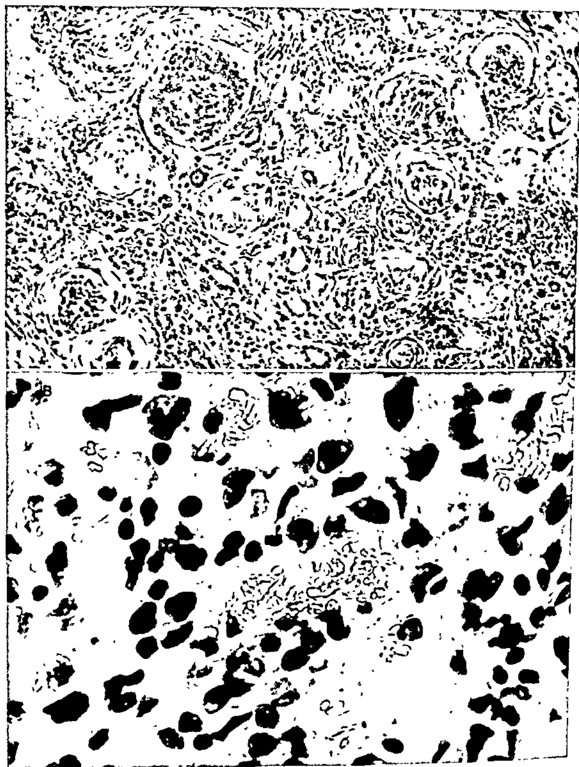
*Cystinosis, Cystinuria and the de Toni-Fanconi Syndrome*

There appears to be a close relationship between the de Toni-Fanconi syndrome (with cystinuria) and the condition of hereditary cystinuria and cystinosis (deposits of crystals of cystine in various organs), although the relationship is not entirely clear Cystinuria is one of the "inborn errors of metabolism" occurring as a familial trait in siblings In young children, cystinuria, which in this age group is likely to be temporary and irregular, is commonly associated with tissue cystinosis and rarely with cystine calculi; in older children, cystinuria tends to be associated with cystine calculi rather than with cystinosis In these older children, therefore, the effects of the cystinosis are usually merely those of calculous pyelonephritis, if any at all (Freudenberg; Russell and Barrie). In the younger children, who are more prone to have cystinosis, the problem is often grave because of characteristically impaired resistance to infection and the likelihood of ultimate renal insufficiency. This age differential corresponds to the deleterious renal effects produced in young rats fed cystine in contrast to the lack of renal damage in older rats (Cox et al., Addis et al ).

No instance of the combination of cystinosis with glycosuria but without renal rickets has been recorded (McCune et al.) Three cases of cystinosis without renal rickets have been collected (McCune et al ), although most instances of cystinosis do have an associated renal rickets In two of the above cases of nonrachitic cystinosis, destruction of glomeruli, tubular atrophy and interstitial fibrosis were described In two cases of cystinosis in siblings, illustrated in plate 206, the renal lesions appear to be a chronic glomerulonephritis, with severe tubular atrophy In the third case, a six year old child, the kidneys show focal glomerular and tubular atrophy confined to no particular zone, and vacuolization in the loops of Henle (plate 205). The vacuolated epithelium did not take the stains for glycogen, although the pattern strongly suggested glycogenic vacuoles The failure to stain positively may well have been on an artefactitious basis in this instance No vascular lesions were present and the focal atrophy of nephrons appeared too limited to have caused serious renal dysfunction There is limited help to be derived from currently available data on the pathology of the kidney in the de Toni-Fanconi syndrome, or cystinosis, but it is apparent that the clinical entity may also occur when the changes are not histologically conspicuous




FIGS. A AND B. *De Toni Fanconi syndrome* (renal rickets, glycosuria, aminoaciduria, hypophosphatemia, etc.) The renal pathology has not been adequately clarified. In this instance of a child, aged 8, there was focal atrophy of individual nephrons, interstitial fibrosis, dense proteid casts (figure A) and glycogen like vacuolization of the descending limbs and loops of Henle (figure B). No cystine crystals were present. (Histologic slides obtained through the courtesy of Dr. J. Gohman, Univ. of Louisville.)




(Legend on facing page.)

## References

ADDIS, T., MACKAY, E. M., AND MACKAY, L. L. The effect on the kidney of the long continued administration of diets containing an excess of certain elements I Excess of protein and cystine J Biol Chem 71: 139-156, 1926-1927

ALBRIGHT, F., AND REIFENSTEIN, E. The parathyroid glands and metabolic bone disease Baltimore, Williams & Wilkins, 1948

COX, G J, SMYTHE, C V, AND FISHBACK, C F The nephropathogenic action of cystine J Biol Chem 82: 95-103, 1929

ELLIS, A, AND EVANS, H Renal dwarfism, report of 20 cases with special reference to its association with certain dilatations of the urinary tract Quart. J Med 26: 231-251, 1933

FANCONI, G Weitere Beiträge zur Cystinkrankheit (Der Amindiabetes) Helvet paediat acta 1: 183-205, 1946

FREUDENBERG, L Cystinosis, Cystine Disease (Lignac's disease) in Children In Advances in Pediatrics, Vol 4 New York, Interscience, 1949, p 265-292

HOTTINGER, A Ueber Cystin-Diathese Ann paediat 166: 257-283, 1941.

—— Zur Cystindiathese Ann Paediat 169: 272-281, 1947

MCCUNE, D. J, MASON, H H, AND CLARKE, H T Intractable hypophosphatemic rickets with renal glycosuria and acidosis (the Fanconi syndrome). Am J Dis Child 65: 81-146, 1943

ROULLET, F Das anatomische Bild der Cystinkrankheit mit Zwergwachs Ann paediat 156: 284-323, 1941

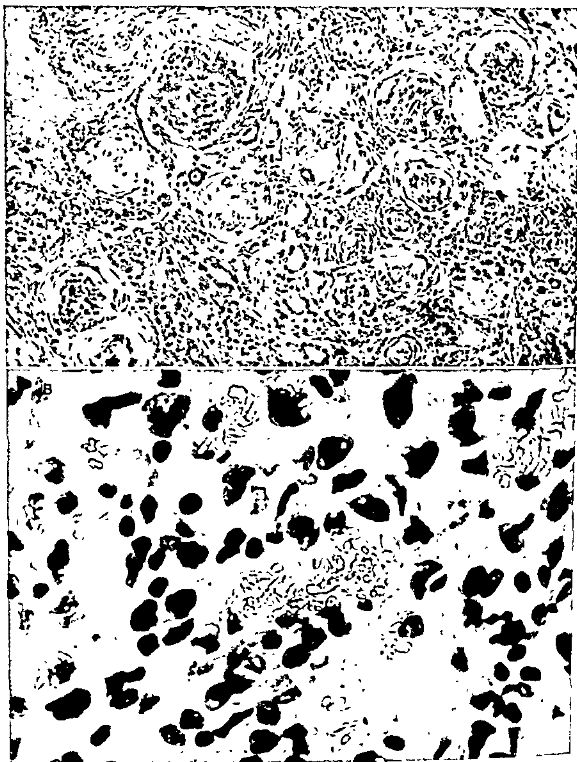
RULE, C, AND GROLLMAN, A Osteonephropathy a clinical consideration of "renal rickets" Ann Int Med 20 63-74, 1944

RUSSELL, D S, AND BARRIE, H J Storage of cystine in the reticulo-endothelial system and its association with chronic nephritis and renal rickets Lancet 2, 899-904, 1936.

DE TONI, G Remarks on the relations between renal rickets (renal dwarfism) and renal diabetes Acta paediat 16, 479-484, 1933

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FIG A *Kidney from a case of cystinosis* with intractable renal rickets in a 7 year old child showing various stages of glomerulitis, glomerular atrophy and tubular atrophy, and marked sclerosis of afferent arterioles and interlobular arteries Renal tubular and interstitial masses of cystine crystals were present and are illustrated in figure B The crystals were present in insufficient numbers to be considered the cause of the renal changes which seem consistent with the diagnosis of chronic sclerosing glomerulonephritis The patient had acidosis, hypophosphatemia and albuminuria with terminal hyperphosphatemia and uremia No glycosuria was recorded Cystine crystals were found in many organs, including lung, liver, adrenals, pancreas, thyroid, intestines, lymph nodes, spleen and testicle A similar condition was found in a sibling (*Histologic slides obtained through the courtesy of B Earl Clark*)




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## References

ADDIS, T., MACKAY, E. M., AND MACKAY, L. L. The effect on the kidney of the long continued administration of diets containing an excess of certain elements. I. Excess of protein and cystine. J. Biol. Chem. 71: 139-156, 1926.

ALBRIGHT, F., AND REIFENSTEIN, E. The parathyroid glands and metabolic bone disease. Baltimore, Williams & Wilkins, 1948.

COX, G. J., SMYTHE, C. V., AND FISHBACK, C. F. The nephropathogenic action of cystine. J. Biol. Chem. 82: 95-101, 1929.

ELLIS, A., AND EVANS, H. Renal dwarfism: report of 20 cases with special reference to the association with certain dilatations of the urinary tract. Quart. J. Med. 2: 231-254, 1933.

FANCONI, G. Weitere Beiträge zur Cystinkrankheit (Der Aminodiabetes). Helvet. paediat. acta 1: 183-200, 1946.

FREUDENBERG, E. Cystinosis, Cystine Disease (Lignac's disease) in Children. In Advances in Pediatrics, Vol. 4. New York, Interscience, 1949, p. 265-292.

HOTTINGER, A. Ueber Cystin-Diathese. Ann. paediat. 156: 257-283, 1941.

— Zur Cystindiathese. Ann. Paediat. 169: 272-281, 1947.

MCCUNE, D. J., MASON, H. H., AND CLARKE, H. T. Intractable hypophosphatemic rickets with renal glycosuria and acidosis (the Fanconi syndrome). Am. J. Dis. Child. 65: 81-146, 1943.

ROUILLER, F. Das anatomische Bild der Cystinkrankheit mit Zwergwuchs. Ann. paediat. 156: 284-323, 1941.

RUTT, C., AND GROSSMAN, A. Osteonephropathy: a clinical consideration of "renal rickets." Ann. Int. Med. 20: 63-76, 1944.

RUSSELL, D. S., AND BARRIE, H. J. Storage of cystine in the reticulo-endothelial system and its association with chronic nephritis and renal rickets. Lancet 2: 899-901, 1930.

DE TONI, G. Remarks on the relations between renal rickets (renal dwarfism) and renal diabetes. Acta paediat. 16: 479-484, 1933.

FIG. [illegible] Kidney from a case of cystinosis with intractable renal rickets in a 7 year old child showing various stages of glomerulitis, glomerular atrophy and tubular atrophy, and marked sclerosis of afferent arterioles and interlobular arteries. Renal tubular and interstitial masses of cystine crystals were present and are illustrated in figure [illegible]. The crystals were present in insufficient numbers to be considered the cause of the renal changes which seem consistent with the diagnosis of chronic sclerosing glomerulonephritis. The patient had acidosis, hypophosphatemia and albuminuria with terminal hyperphosphatemia and uremia. No glycosuria was recorded. Cystine crystals were found in many organs including lung, liver, adrenals, pancreas, thyroid, intestines, lymph nodes, spleen and testicle. A similar condition was found in a sibling. (Histologic slides obtained through the courtesy of B. Earl Clark.)

PLATE 206. CYSTINOSIS



(Legend on facing page.)

## References


Addis, T., MacKay, E. M., and MacKay, L. L. The effect on the kidney of the long continued administration of diets containing an excess of certain elements. I. Excess of protein and cystine. J. Biol. Chem. 71: 139-156, 1926-1927.

Albright, F., and Reifenstein, E. The parathyroid glands and metabolic bone disease. Baltimore, Williams & Wilkins, 1948.

Cox, G. J., Smythe, C. V., and Fishback, C. F. The nephropathogenic action of cystine. J. Biol. Chem. 82: 95-101, 1929.

Ellis, A., and Evans, H. Renal dwarfism, report of 31 cases with special reference to its association with certain dilatations of the urinary tract. Quart. J. Med. 25: 231-251, 1933.

Fanconi, G. Weitere Beiträge zur Cystinkrankheit (Der Aminodiabetes). Helvet. paediat. acta 1: 183-203, 1946.

Freudenberg, E. Cystinosis. Cystine Disease (Lignac's disease) in Children. In Advances in Pediatrics, Vol. 4. New York: Interscience, 1949, p. 265-292.

Hottinger, A. Ueber Cystin Diathese. Ann. paediat. 156: 257-283, 1941.

—— Zur Cystindiathese. Ann. Paediat. 169: 272-281, 1947.

McCune, D. J., Mason, H. H., and Clarke, H. T. Intractable hypophosphatemic rickets with renal glycosuria and acidosis (the Fanconi syndrome). Am. J. Dis. Child. 65: 81-146, 1943.

Rotter, F. Das anatomische Bild der Cystinkrankheit mit Zwergwuchs. Ann. paediat. 156: 284-323, 1941.

Rule, C., and Grollman, A. Osteonephropathy: a clinical consideration of "renal rickets." Ann. Int. Med. 20: 63-71, 1944.

Russell, D. S., and Barrie, H. J. Storage of cystine in the reticulo-endothelial system and its association with chronic nephritis and renal rickets. Lancet 2: 899-904, 1936.

de Toni, G. Remarks on the relations between renal rickets (renal dwarfism) and renal diabetes. Acta paediat. 16: 479-484, 1933.


Fig. A. *Kidney from a case of cystinosis* with intractable renal rickets in a 7 year old child showing various stages of glomerulitis, glomerular atrophy and tubular atrophy, and marked sclerosis of afferent arterioles and interlobular arteries. Renal tubular and interstitial masses of cystine crystals were present and are illustrated in figure B. The crystals were present in insufficient numbers to be considered the cause of the renal changes which seem consistent with the diagnosis of chronic sclerosing glomerulonephritis. The patient had acidosis, hypophosphatemia and albuminuria with terminal hyperphosphatemia and uremia. No glycosuria was recorded. Cystine crystals were found in many organs including lung, liver, adrenals, pancreas, thyroid, intestines, lymph nodes, spleen and testicle. A similar condition was found in a sibling. (Histologic slides obtained through the courtesy of B. Earl Clark.)

# 13. Diseases of Vessels

### Classification of Vascular Diseases

Capillaries

- Diabetic glomerulosclerosis
- Amyloidotic glomerulosclerosis
- Fat embolization

Arterioles

- [illegible]

Arteries

- Arteriosclerosis
- Periarteritis nodosa
- Scleroderma
- Bacterial arteritis
- Thromboangiitis obliterans
- Bilateral cortical necrosis
- Embolization and thrombosis

Veins

- Thrombosis
- Thromboangiitis obliterans

As will be indicated, it is possible for more than one of the above conditions to occur in the same kidney

### Arterial (Senile) Nephrosclerosis

The arteriosclerotic or senile contracted kidney *is not of itself responsible for hypertension* or renal insufficiency except in rare instances of unusual renal atrophy

#### *Pathology*

*Gross appearance*

The kidneys are about of normal size and are characterized by thickened capsules adherent particularly over wedge-shaped depressed atrophic scars Such scarred areas correspond to the renal parenchyma that has undergone slow ischemic atrophy as a result of sclerosis and narrowing of the lumen of the large branches of the renal artery (plate 207)

*Histologic appearance*

Histologically, sclerosis involves the major arterial branches but may extend to the arcuate arteries In addition, there may be evidence of *ischemic atrophy of the* parenchyma particularly in the subcapsular regions. The foci of atrophy include lymphocytic infiltration about hyalinized fibrotic glomerular scars and atrophic tubules (plate 208). According to some observers, *the scarred glomeruli may eventually* disappear (Staemmler) Small cortical cysts, thought to be derived from Bowman's capsules, are frequently present. Areas of cortical atrophy, especially when accompanied by abundant lymphocytic infiltration, *may resemble* pyelonephritic scars Naturally the arteriosclerotic kidney may be complicated by arteriolosclerosis, pyelonephritis, embolization, thrombosis, amyloidosis and other conditions Often the parenchyma may show practically no change, despite conspicuous arteriosclerosis

Apart from the atrophic glomeruli in the scarred areas, scattered completely fibrotic glomeruli are usually found. "Axial" or intercapillary thickening of the glomeruli has been described as part of the senile kidney (Kimmelstiel) There appears to be ample histogenetic reason to believe that the mesangial thickening referred to is actually a *sclerosis of glomerular capillaries* Moreover the association of this glomerulosclerosis—whatever its histogenesis—with the uncomplicated aging process cannot be confirmed. These glomerular tufts are indistinguishable from those glomeruli seen in hypertensive patients (McGregor), an observation *convincingly documented by* MacCallum

Although the uncomplicated arteriosclerotic kidney presents no problem, as indicated, there may be superimposed on such a kidney any grade of arteriolosclerosis with hypertension and renal insufficiency. Occasionally an eccentric sclerotic plaque partially occluding the ostium of a main renal artery appears to have been associated with and possibly responsible for the development of hypertension, presumably after the fashion of unilateral experimental occlusion of the renal artery in the rat. In isolated instances, the hypertension may be re-

lated to the abundant parenchymal atrophy that may occur in the kidney secondary to marked renal arteriosclerosis.

## ARTERIOLAR (BENIGN) NEPHROSCLEROSIS

### Introduction

*Benign nephrosclerosis* refers to the renal lesion observed in association with the clinical complex known as *essential, idiopathic,* or *benign hypertension.* Essential hypertension is predominantly a disease of the fifth, sixth, and seventh decades of life, although rare instances even in the teens are recorded. Most series indicate that the disease is somewhat more common in females (Wetherby, Master et al.). Hypertension is rare among the Orientals, and apparently also among Negroes living in Africa. On the other hand, there appears to be a considerably higher incidence of essential hypertension among Negroes subjected to the competitive stress of an urban environment of the United States than among the white population in a similar situation. Similarly, the incidence of hypertension among the West Indian Negroes living in Panama is considerably greater than among the native Panamanians (Kean). There seems to be a strong hereditary or, at least, familial element in essential hypertension. This, too, may be merely a reflection of environmental strain. The great majority of people with hypertension are said to fall into the sthenic constitutional habitus, with definite obesity an unquestionable added hazard.

### Clinical Aspects

The clinical picture of essential hypertension is variegated. The onset may be vague, and may be suggested by vasomotor and emotional instability characterized by blushing, sweating, fits of anger, lacrimation, excessive salivation, and sudden rises in blood pressure, that is, the *diencephalic syndrome* occurring in young women particularly (Page). Vertigo, tinnitus, insomnia, paresthesias, visional disturbances or pains in the extremities may be additional early symptoms. Frequently, evidence of cardiac insufficiency, such as anginal attacks, precordial oppression, dyspnea on exertion, or cardiac asthma, is the initial clue. In some instances, an actual apoplectic stroke may be the first indication of hypertension. Often, however, the first sign of hypertension is disclosed by the sphygmomanometer in a routine physical examination.

Generally, systolic pressures of 150 mm. and diastolic pressures of 90 mm. are considered the threshold of hypertension. Some insurance companies prefer to reduce their risk by adopting a lower standard of 140/80 for any age (Daley et al.). The old formula that the normal blood pressure for a given adult age may be computed by adding the age to 100 is no longer regarded as accurate (Robinson and Brucer, Robinson et al.). Pressures of 140/90 mm. Hg or greater occur in about 50 per cent of males and 60 per cent of females over the age of forty (Bell). With the lower limit of 150/90 mm. Hg, hypertension was found in the fifth decade in 25 per cent of men and 33 per cent of women, in the sixth decade, in 40 per cent of men and 50 per cent of women. Two-thirds of women past the sixth decade and the same number of men past the seventh decade had hypertension (Master et al.). These figures concern a somewhat selected sample of population, but they and other series indicate that nearly half the population over 50 years of age have hypertension according to the above definitions and the majority are without symptoms. About 80 per cent of people who die of hypertensive disease are over the age of 50. Moreover, about three-fourths of patients with hypertension die of some other disease (Bell).

When blood pressure fluctuates, there is some tendency to choose the lowest reading especially if it occurs under what are considered "relaxed conditions." However, such optimism appears unwarranted. It is becoming increasingly clear that individuals whose blood pressure reaches an abnormal level under any circumstances are predisposed to the subsequent development of frank hypertensive disease.

Pressures of 200 mm. systolic and 110 mm. diastolic are common in this disease. In association with the hypertension the patient may show evidence of cardiac hypertrophy and insufficiency, emphysema, coronary arteriosclerosis, hypertensive encephalopathy and in a small percentage of cases renal insufficiency. This last feature is to be stressed because, although the

pathologic changes of the kidney are emphasized in the study of essential hypertension, only about 7 per cent of the cases die in uremia.

### *Prognosis*

In essential hypertension attempts to correlate prognosis with the height of blood pressure are often not reliable Although it is true that the level of hypertension and the complications therefrom in many cases vary with its duration, there are too many exceptions to warrant such a blanket rule. In a greater number of instances, the pressure may remain constant for years—10 to 15 or longer—and in others it rises slowly and in still others, rapidly. The elevated diastolic pressure is particularly important in estimating the gravity of prognosis The mortality from cardiac failure or from clinically apparent vascular changes in other organs need have no direct relation to the height of the hypertension On the other hand, Foa, Foa and Peet state that the determination of the ratio of the width of the wall to the size of the lumens (W/L) of arterioles in biopsy specimens of skeletal (intercostal) muscle is significant in determining the prognosis of patients with essential hypertension or hypertension secondary to chronic nephritis: the greater the ratio, the worse the prognosis, of course

The early age of onset of the hypertension influences the prognosis adversely, hypertension initiated in middle age or later tends to progress more torpidly Although essential hypertension occurs somewhat more frequently in women, its course is prone to be more severe in men Diabetes mellitus after middle age seriously increases the likelihood of the development of hypertension The reason for this predisposition has not been satisfactorily explained on any organic basis, but the suggestion has been made that the sclerosis of the efferent arteriole may play a role (Allen). The efferent arteriole is presumed to be constricted by angiotonin in experimental hypertension thereby raising intraglomerular tension; in the kidneys of hypertensives with diabetic glomerulosclerosis the efferent arteriole is often organically narrowed (plate 241E, F). As stated, obesity is a real hazard to hypertensive patients and, conversely, reduction in weight of such obese patients has been found to be followed by decrease in blood pressure (Walker; Freed; Levy et al ; Robinson et al.).

### *Differential Diagnosis*

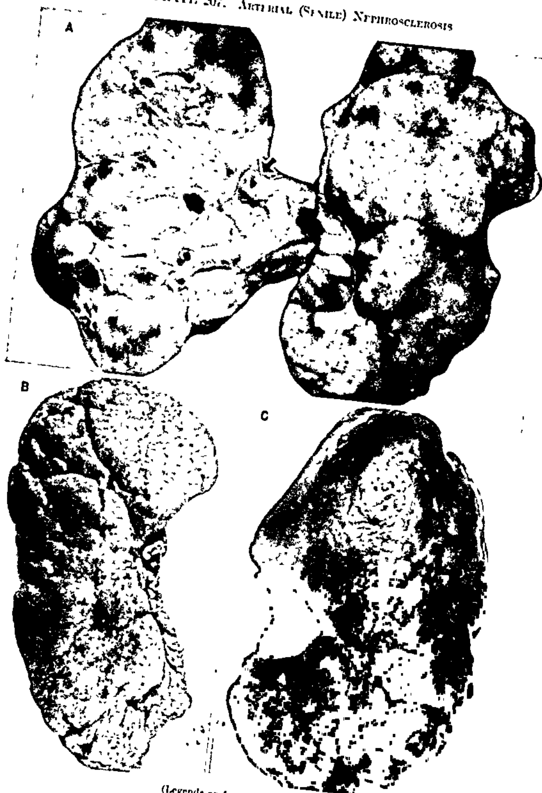
The picture of essential hypertension may be simulated by chronic glomerulonephritis, congenital polycystic kidneys, coarctation of the aorta, chronic pyelonephritis, pituitary basophilism, diencephalic lesions, adrenal hyperplasia, adrenal cortical adenoma or carcinoma, pheochromocytoma, renal amyloidosis, periarteritis nodosa, renal hypoplasia, neoplasms of the kidney, healed infarcts, gout nephritis and unilateral narrowing of the main renal artery by a sclerotic plaque, thrombus, or extrinsic mass In these cases, as in essential hypertension, the *diastolic* as well as the systolic pressure is elevated. It is this criterion that categorically separates these conditions from aortic insufficiency, arteriosclerosis, hyperthyroidism, and heart block with bradycardia in which the diastolic pressure is not elevated despite the rise in systolic pressure

### *Urine*

In most patients with essential hypertension there is no abnormal urinary finding When abnormalities occur, they may be the result of cardiac rather than renal failure. In the former case, *urinary volume* diminishes but concentrating ability is not disturbed, in the latter, polyuria occurs as a compensatory attempt against the loss in concentrating power which for years may be associated with specific gravity no higher than *1.015. The failure to com*pensate for lack of concentration by increased

FIGS A, B, AND C *Arterial nephrosclerosis* characterized by sclerotic narrowing of the renal artery (arrow) and its main branches with resultant deep irregular parenchymal scars correspond-

sclerosis (plate 186A)




(Legends on facing page.)

volume may mean cardiac impairment or dangerously progressive renal dysfunction. Nocturia occurs commonly in patients with essential hypertension either because the cardiac strain is eased at night, the circulation improved and urinary volume increased, or because, if function of the kidneys is impaired, the increased volume must be maintained even through the night to make up for diminished concentrating capacity.

*Albuminuria* may be present or absent in essential hypertension. When present it is usually slight in amount and is due to cardiac decompensation or to minor glomerular damage. Abundant albuminuria in an elderly patient with hypertension should lead to a suspicion of diabetic glomerulosclerosis, or, much more remotely, amyloidosis. Fishberg points out that the renal threshold for sugar may be elevated in essential hypertension so that the diagnosis of diabetes mellitus may be overlooked if complete reliance is placed on the absence of glycosuria.

The *sediment* may be entirely negative, or a few granular casts and leukocytes may be present. Isolated red blood cells in the urine may be the result of passive congestion of the kidney; if abundant, hematuria may indicate the malignant phase of the disease.

A low *filtration fraction* has been noted in early, moderately advanced and late stages of glomerulonephritis in contrast to the elevated filtration fraction of benign nephrosclerosis with hypertension (Cargill). The implication is that the increased filtration fraction in hypertension is caused by constriction of the efferent arteriole. Cargill observed, however, that as the vascular disease progressed, there was a decrease in the filtration fraction which he attributed to the progressive afferent arteriolosclerosis counterbalancing the effect of efferent arteriolosclerosis.

*Pathology of Arteriolar (Benign) Nephrosclerosis*

*Gross appearance*

The arteriolosclerotic kidneys of benign nephrosclerosis vary in size depending on the duration and severity of the disease. Early the kidneys may be slightly larger than normal principally because of the congestion; in the late stage, they may shrink to less than half normal size. In Bell's series of 315 cases of benign nephrosclerosis from patients with essential hypertension, the combined weight of the kidneys was as shown in table 8. In other words, in about 21 per cent, there was no reduction in the size of the kidneys and in almost a third of the cases, there was marked contraction. There is no relationship between the weights of the kidneys and the heart.

TABLE 8 —*Combined Weight of Kidneys in Bell's cases**

| *Combined Wt of Kidneys (Gm)* | *% of 315 cases* |
|---|---|
| 60–99 | 1 6 |
| 100–199 | 28 9 |
| 200–299 | 48 6 |
| 300–399 | 18 4 |
| 400–475 | 2.5 |

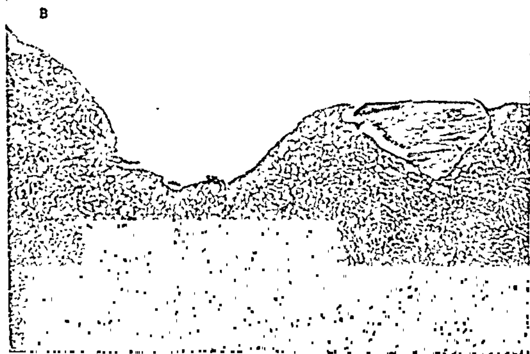
* "Primary hypertension"

In the initial stages, the surface may be smooth so that macroscopic findings may be deceptive (plate 209A). The surface very soon acquires a diffuse fine granularity that has been compared in appearance to scotch grain leather. In general, these kidneys have a purple-red hue so that they have been designated the "red" kidneys in contrast to the "white" kidneys of chronic glomerulonephritis (plate 67A). The purple-red color is produced essentially by the hyperemia particularly of the atrophic "troughs" separating the yellow-grey normal or hypertrophied tubules forming the elevated granules (plate 209B). The regularity of the

FIG A *Arteriosclerosis of arcuate artery* in arterial nephrosclerosis, with associated parenchymal atrophy.

FIG. B *Cortical depression and subcapsular cortical cyst* common in arterial nephrosclerosis. In this case, arteriolosclerosis of the afferent arterioles, as well as hypertension, were absent. In other words, even marked renal arteriosclerosis may occur with or without renal arteriolosclerosis. Renal arteriosclerosis can only rarely be considered causally related to hypertension or renal insufficiency.




(Legends on facing page.)

volume may mean cardiac impairment or dangerously progressive renal dysfunction Nocturia occurs commonly in patients with essential hypertension either because the cardiac strain is eased at night, the circulation improved and urinary volume increased, or because, if function of the kidneys is impaired, the increased volume must be maintained even through the night to make up for diminished concentrating capacity

*Albuminuria* may be present or absent in essential hypertension When present it is usually slight in amount and is due to cardiac decompensation or to minor glomerular damage. Abundant albuminuria in an elderly patient with hypertension should lead to a suspicion of diabetic glomerulosclerosis, or, much more remotely, amyloidosis. Fishberg points out that the renal threshold for sugar may be elevated in essential hypertension so that the diagnosis of diabetes mellitus may be overlooked if complete reliance is placed on the absence of glycosuria.

The *sediment* may be entirely negative, or a few granular casts and leukocytes may be present Isolated red blood cells in the urine may be the result of passive congestion of the kidney, if abundant, hematuria may indicate the malignant phase of the disease

A low *filtration fraction* has been noted in early, moderately advanced and late stages of glomerulonephritis in contrast to the elevated filtration fraction of benign nephrosclerosis with hypertension (Cargill) The implication is that the increased filtration fraction in hypertension is caused by constriction of the efferent arteriole Cargill observed, however, that as the vascular disease progressed, there was a decrease in the filtration fraction which he attributed to the progressive afferent arteriolosclerosis counterbalancing the effect of efferent arteriolosclerosis

### *Pathology of Arteriolar (Benign) Nephrosclerosis*

*Gross appearance*

The arteriolosclerotic kidneys of benign nephrosclerosis vary in size depending on the duration and severity of the disease. Early the kidneys may be slightly larger than normal principally because of the congestion, in the late stage, they may shrink to less than half normal size In Bell's series of 315 cases of benign nephrosclerosis from patients with essential hypertension, the combined weight of the kidneys was as shown in table 8 In other words, in about 21 per cent, there was no reduction in the size of the kidneys and in almost a third of the cases, there was marked contraction There is no relationship between the weights of the kidneys and the heart

TABLE 8 —*Combined Weight of Kidneys in Bell's cases**

| *Combined Wt of Kidneys (Gm )* | *% of 315 cases* |
|---|---|
| 60–99 | 1 6 |
| 100–199 | 28 9 |
| 200–299 | 48 6 |
| 300–399 | 18 4 |
| 400–475 | 2 5 |

* "Primary hypertension"

In the initial stages, the surface may be smooth so that macroscopic findings may be deceptive (plate 209A). The surface very soon acquires a diffuse fine granularity that has been compared in appearance to scotch grain leather. In general, these kidneys have a purple-red hue so that they have been designated the "red" kidneys in contrast to the "white" kidneys of chronic glomerulonephritis (plate 67A) The purple-red color is produced essentially by the hyperemia particularly of the atrophic "troughs" separating the yellow-grey normal or hypertrophied tubules forming the elevated granules (plate 209B). The regularity of the

FIG A *Arteriosclerosis of arcuate artery* in arterial nephrosclerosis, with associated parenchymal atrophy

FIG B *Cortical depression and subcapsular cortical cyst* common in arterial nephrosclerosis In this case [illegible] were absent In o[illegible] sclerosis [illegible] renal insufficiency




B

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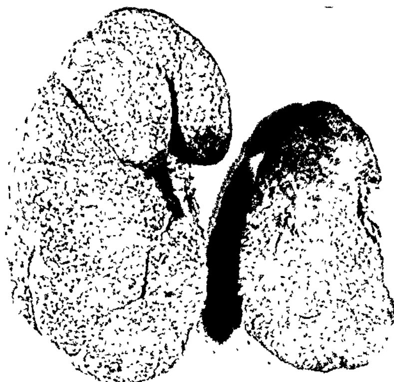






FIG. A. *Kidneys of arteriolar or benign arteriosclerosis* associated with hypertension and showing slight (left) and severe (right) degrees of contraction, along with the characteristic, fine granularity secondary to the sclerosis of afferent arterioles and interlobular arteries

FIG B *Arteriolar (benign) nephrosclerosis* associated with hypertension, illustrating the histologic picture *of a typical surface granule characterized by crests of dilated tubules alternating* with troughs of atrophic tissue The sclerosis of interlobular arteries and afferent arterioles may be discerned (Elastica-van Gieson stain)

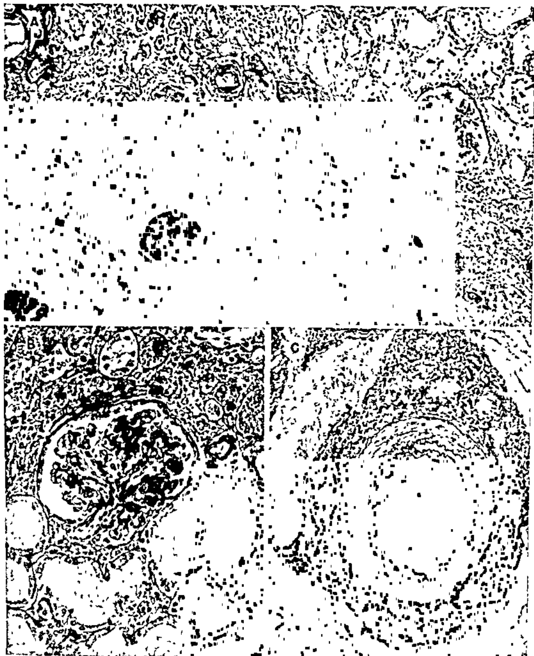
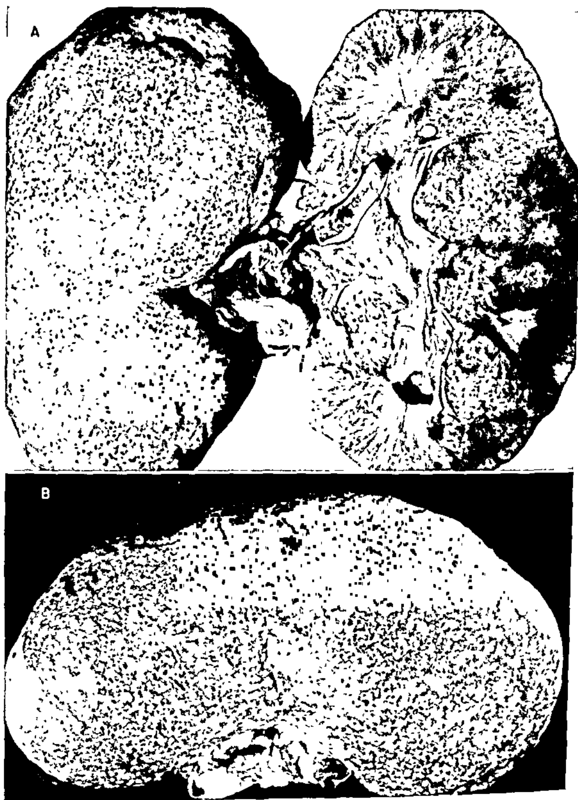



FIG A *Arteriolar nephrosclerosis* showing atrophic and hyperplastic nephrons, scarred as well as essentially spared glomeruli, and sclerosis of afferent arterioles and interlobular arteries (Elastica–van Gieson stain)

FIG B *"Hypertensive glomerulus"* of arteriolar nephrosclerosis consisting of sclerotic glomerulus with afferent arteriolosclerosis Portions of atrophic and hyperplastic nephrons are also included

FIG C *Hyperplastic sclerosis* is often associated with the benign nephrosclerosis of hypertension and is characterized by reduplication of the internal elastic lamina (Elastica–van Gieson stain)




d
s

cating a benign nephrosclerosis of much longer duration in (B). (A A F.I P Acc 46,80)

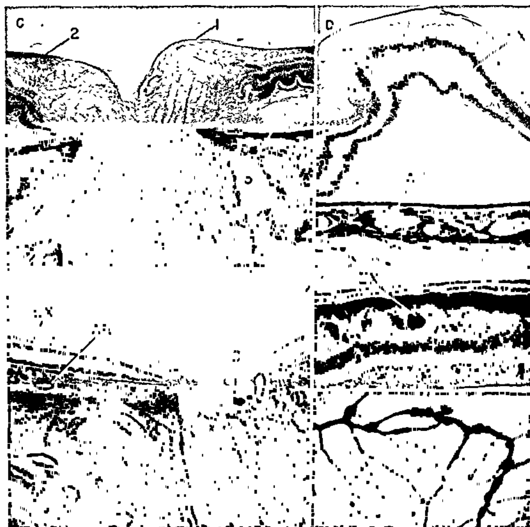



FIG C *Hypertensive neuroretinopathy of malignant hypertension* showing (1) papilledema, (2) retinal hemorrhage, and (3) subretinal exudate

FIG E *Benign nephrosclerosis* Hypertensive retinopathy with normal disc and nerve (D), exudate (Ex) ophthalmoscopically star shaped about macula and arteriolosclerosis (Ar) of choroid

FIG D *Hypertensive neuroretinopathy* of malignant hypertension showing retinal detachment, retinal exudate (Ex), and arteriolosclerosis of choroid (Ar)

FIGS F AND G *Diabetic retinopathy* with retinal exudate (Ex) in figure F, and arteriolosclerotic segmental thickenings in figure G (Arch Ophth *44* 539, 1950, Am J Ophth *32* 487, 1949)

(These photomicrographs were obtained through the courtesy of Dr David Wexler, New York City)

mal lesions were found in fully 50 per cent of cases

*Objections* to this latter study have been raised on the grounds that a small biopsy specimen of kidney might not be representative, since, it was declared, sclerosis of renal arterioles is segmented with intervening normal areas. The objection *in this instance is not as* serious as it might seem to be Actually, afferent arteriolosclerosis of hypertension spares very few nephrons and is sufficiently diffuse to be seen in almost any section in which the arteriole is present What the findings of this biopsy material indicate is that hypertension may precede significant organic renal vascular change *This* conclusion does not negate the possibility of *functional* renal arteriolar change antedating the hypertension In any case, the fact still remains that with long-standing hypertension, one may anticipate diffuse afferent arteriolosclerosis at postmortem Furthermore, it is usually possible to estimate the degree of hypertension from the degree of arteriolosclerosis observed in postmortem sections of the kidney. Moritz and Oldt state that in about 12 per cent of cases a minor degree of "arteriolosclerosis" may occur in the absence of a history of hypertension In our experience, *diffuse* afferent *arteriolosclerosis rarely occurs* without associated hypertension In general, the extent of the cardiac hypertrophy parallels the degree of afferent arteriolosclerosis.

*Juxtaglomerular Apparatus in Hypertension· In connection* with changes in the renal arterioles, mention should be made of the observations of the juxtaglomerular apparatus in hypertension Detailed data about granularity, fibrillarity and hyperplasia have been published regarding these cells whose role is still ill defined Their strategic location at the vascular pole of the glomerulus has led to the postulation that they exert control over the caliber of the afferent and efferent arterioles. The juxtaglomerular apparatus, however, is normally variable in size and histology in diffe ent nephrons Precise micrometric determin tions in serial sections of a statistically si nificant sample of these cells in controlled ar abnormal kidneys have *not been done. Ther* fore conclusions regarding their hyperplasi size and quality must be questioned

*Tubules:* The tubules in the arteriolosclerot kidney show evidence of atrophy, hypertroph and hyperplasia *in much the same way as* i chronic glomerulonephritis In the latter, how ever, the compensatory changes of hypertroph and hyperplasia are more marked In additior there is considerably more blockage of the dis tal convoluted tubules by casts and conse quently greater hydronephrotic distortion ir the nephritic kidney. Lipid and hyaline drop *let degeneration of the epithelium of the prox* imal convoluted tubules are common focal find ings.

*Interstitium* As portions of the nephron atrophy, there occurs a concomitant interstitial, *well vascularized, argyrophilic fibrous replace*ment associated with infiltrations of lymphocytes, plasma cells and histiocytes. This interstitial reaction occurs early as wedge-shaped areas between the surface granules and later involves other portions of the cortex

## *Extrarenal Changes in Benign Nephrosclerosis*

### *Heart*

*Although patients* with hypertension are likely to have enlarged hearts, particularly with left ventricular hypertrophy, there is no direct correlation between the level of the blood pressure, the size of the kidneys, and the size of the heart Remarkable surprises are occasionally encountered in the form of normal sized or only *slightly* enlarged *hearts in* patients with moderate, longstanding hypertension As a rule however, hypertension of some duration and constancy is accompanied by cardiac enlargement. In those cases of hyperten-

Fig. A *Small hemorrhagic infarct* of accelerated (malignant) nephrosclerosis The blood in the tubules illustrates one basis for the hematuria in malignant nephrosclerosis

Fig B *Interstitial hemorrhage, necrotizing afferent arteriolosclerosis and necrotizing glomerulitis* of accelerated nephrosclerosis superimposed on benign arteriolar nephrosclerosis The necrotizing glomerulitis is another mechanism for hematuria in malignant nephrosclerosis

PLATE 213. ACCELERATED (MALIGNANT) NEPHROSCLEROSIS



(Legends on facing page.)

sion in which renal insufficiency develops, about 95 per cent of hearts weigh more than 400 Gm, and about 75 per cent weigh more than 500 Gm; in hypertensive women, the average weight of the heart is about 75 Gm less than in males (Bell). There is no correlation between the level or duration of hypertension and the degree of coronary arteriosclerosis or coronary arteriolosclerosis. Whether or not the sclerosis of coronary vessels is caused by or is correlated with hypertension, nevertheless, it is often present in the age group afflicted with hypertension. Therefore, given two hearts with an equivalent degree of coronary arteriosclerosis, the one made larger by hypertension is obviously more likely to develop coronary insufficiency. The reason is, of course, that the myocardial muscle mass is more apt to outstrip its blood supply in the larger heart. In this same connection, it is to be noted that cardiac failure in essential hypertension may be precipitated by sudden additional cardiac stresses such as are produced by an abrupt rise in blood pressure, acute infections and possibly unusual exertion. Considerable medicolegal polemics have centered about the last mentioned factor without appreciable resolution of the problem.

*Brain*

Patients with hypertension may develop signs and symptoms as a result of what has been termed *hypertensive encephalopathy*. These include transient palsies, pareses, aphasias and amaurosis as well as headache, vertigo, incoherence and even dementia. About 7 to 14 per cent of patients with hypertension develop fatal cerebral hemorrhage (Paullin et al.; Janeway). Conversely it has been found that hypertension occurs in over 93 per cent of patients with massive cerebral hemorrhage not due to local causes such as trauma, aneurysm or neoplasms (Lippmann). Many of the evanescent symptoms are due to arterial and arteriolar sclerosis with areas of encephalomalacia or less marked foci of parenchymal degeneration.

*Eye*

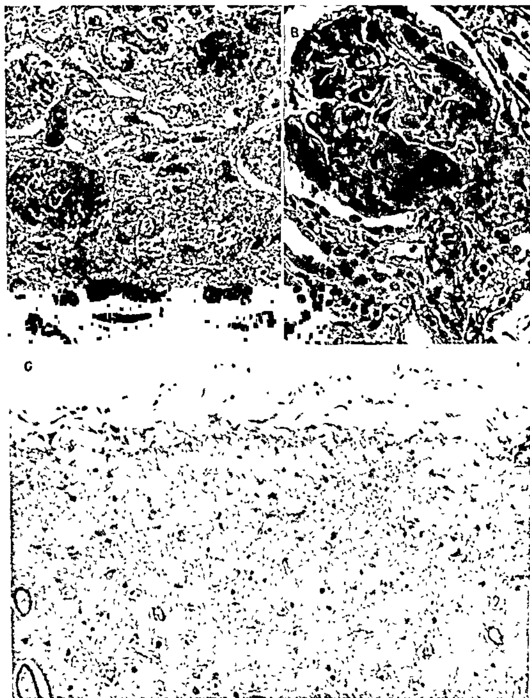
Fundal changes are common in essential hypertension, and are of great diagnostic and prognostic importance. Marked retinal arteriosclerosis and arteriolosclerosis, with tortuosity of the vessels, arteriovenous compression and "silver-wire" appearance, and "hard" white spots (vs. "cotton-wool" exudates) are the principal ophthalmoscopic findings in hypertension, and are absent, as a rule, in patients with merely generalized arteriosclerosis and normal blood pressure. The presence of retinal arteriosclerosis indicates that *hypertension (of whatever etiology)* has been present a considerable time, and is an unfavorable prognostic sign, except in patients with diabetes mellitus. In diabetes, this sign is not necessarily ominous. Arteriosclerotic retinopathy is not as grave a prognostic indication as is hypertensive neuroretinopathy, which it may closely simulate. The latter is characterized by papilledema, "cotton-wool" exudate, hemorrhages, and sclerosis of arteries and arterioles (plate 211C, D, E, F, G). Arteriosclerotic retinopathy or hypertensive neuroretinopathy may occur also in cases of chronic glomerulonephritis with hypertension.

*Lungs*

Passive pulmonary congestion with hemoptysis, rarely of a severe degree, may occur with essential hypertension. Pulmonary emphysema is a common complication and, of course, adds to the myocardial strain.

*Endocrine glands*

None of the endocrine glands shows a change that can be related to essential hypertension with the possible exception of the adrenal glands. It has been stated (Rinehart et al.) that the adrenal glands in hypertension weigh more than in a control group. This observation, which still lacks adequate statistical confirmation in view of Dempsey's data, has acquired



FIGS A AND B *Malignant nephrosclerosis* with hemorrhagic infarction of glomeruli, hemorrhage in tubules, interstitium (A), and juxtaglomerular apparatus (B)

FIG C *Hypertensive encephalopathy* was characterized in this instance by cerebral edema, and sclerosis of small arteries and arterioles

an added interest in view of Selye's emphasis on the role of the adrenal corticoids in the production of hypertension and nephrosclerosis A comprehensive and critical review of the evidence for the relationship of the adrenal cortex to hypertension has been written by Sapeika.

## Malignant Nephrosclerosis

### *Introduction*

The term "malignant nephrosclerosis" has been applied to the characteristic renal changes which reflect the clinical counterpart referred to as "malignant hypertension" The latter term was introduced by T. Fahr to designate a disease entity of fulminant hypertension and uremia. It is now clear that malignant hypertension and malignant nephrosclerosis do not represent a disease *sui generis* but rather a complication of one of several basic diseases that have hypertension as a common denominator For example, the clinical, as well as the histologic, features of malignant hypertension may be superimposed not only on those of essential hypertension, but also on chronic glomerulonephritis, chronic pyelonephritis, pheochromocytoma, the Cushing syndrome of pituitary basophilism, adrenal cortical hyperplasia or neoplasia, and even amyloidosis Rarely, the malignant nephrosclerosis develops so suddenly, and is so fulminant that it masks an underlying benign nephrosclerosis There has been much discussion as to whether or not, as Goldblatt (1938) believes, renal failure, or some unknown humoral factor, must accompany the hypertension in order to produce the necrotizing arteritis of malignant hypertension The evidence appears to be in favor of the theory that hypertension alone, particularly an elevated diastolic pressure (Fishberg) may cause the necrotizing vascular change (Wilson and Byrom) The observation of vascular necrosis in association with pheochromocytomas and with the experimental injection of adrenalin (Waters) is additional evidence for the latter point of view.

### *Clinical Picture*

Malignant hypertension is a complication that occurs in a somewhat younger age group than does the essential hypertension; it is found predominantly in the fourth, fifth, and sixth decades. Rarely, the typical clinical and pathologic picture of malignant hypertension is seen in children The organs illustrated in plates 221 and 222 are from a child six years of age whose malignant nephrosclerosis was superimposed on a chronic glomerulonephritis. Another remarkable case, reported by Kennedy and Barker, was a seven year old girl with a malignant hypertension associated with unilateral chronic pyelonephritis. Her blood pressure was $\frac{170-225}{110-178}$ and there was extensive hypertensive retinopathy.

The symptoms of malignant hypertension are those of rather abrupt onset of increased intracranial pressure as well as of renal insufficiency. The heightened intracranial pressure, simulating an intracranial tumor, may be manifested by nausea, vomiting, headache, stiffness of the neck, visual impairment, hypertensive neuroretinopathy with papilledema, retinal exudates and hemorrhages, convulsions and coma The papilledema, which may reach 6 diopters, is a most reliable indication that the patient has progressed into the malignant phase of hypertension and may even precede the urinary changes such as albuminuria and hematuria. The papilledema may be unilateral for a time.

As stated, hypertensive neuroretinopathy is a most serious prognostic sign and, according to Fishberg, occurs in practically every case of malignant nephrosclerosis Chasis and Goldring, however, disagree with Fishberg on this point, they found the neuroretinopathy absent in 23 per cent of 68 patients with malignant nephrosclerosis. Exophthalmus may also be present and is presumed to be due to the hypertensive encephalopathy. The spinal fluid pressure is usually elevated, occasionally to as high

as 500 mm of water. Most cases of malignant hypertension terminate in uremia

The abrupt development of the phase of malignant hypertension is marked by gross, painless hematuria in about 20 per cent of cases and persistent microscopic hematuria in about 50 per cent (Goldring and Chasis) In some instances the glomeruli do not become focally necrotic and the hemorrhages come from altered arterioles within the renal interstitial tissue In these cases the blood, exceptionally, may not reach the urine Undoubtedly not all the hematuria is the direct mechanical result of necrosis of vessels or of glomeruli, but some is the consequence of the hemorrhagic diathesis commonly observed in uremic patients

### *Pathology of Malignant Nephrosclerosis*

#### *Gross appearance*

The pathologic changes in the kidneys of patients with malignant hypertension obviously vary with the nature of the disease that preceded the malignant phase In other words, as already indicated, the macroscopic features of malignant nephrosclerosis may be added to a kidney showing benign nephrosclerosis, chronic pyelonephritis, and even to kidneys from patients with a pheochromocytoma Most often, however, the basic picture is that of a benign nephrosclerosis in which there has been little contraction (plate 211, 212A), occasionally the granulations are well marked It is of interest that the kidneys of malignant nephrosclerosis are rarely very much shrunken, few weigh less than 120 Gm each In other words, for reasons unknown, the very severity of the underlying benign vascular sclerosis may be responsible for sparing the kidney a superimposed malignant nephrosclerosis The color of the kidneys with malignant nephrosclerosis is brownish or greyish red, the color commonly associated with "vascular" kidneys The principal macroscopic feature that suggests the diagnosis are the "flea-bite" or punctate pin-head sized hemorrhages on the surface of a granular kidney

#### *Histologic appearance*

Histologically, the essential changes are found especially in the interlobular arteries and the portions of the vascular tree distal to them The arterial and arteriolar changes indicative of the malignant phase are these: (1) marked intimal thickening with increase in intimal fibroblasts, edema and lamination of intimal collagen, (2) fibrinoid necrosis of the vascular wall, and (3) the presence of red blood cells within the wall of the vessel (plates 215, 216)

The increased cellularity (fibroblasts as well as leukocytes), edema and lamination of the intima reflect an *acceleration* of the process of vascular sclerosis which, in benign nephrosclerosis, is characterized by a denser, more hyaline and less cellular intima Karyorrhexis of the intimal fibroblasts and leukocytes is a common finding (plate 215A, B).

The fibrinoid necrosis may extend from the afferent arteriole directly into the glomerular capillaries so that foci of fused, granular, degenerated, smudgy, fibrinoid masses are often seen close to the hilum of the glomeruli (plate 214A, B) Thrombosis of small vessels is common (plate 218) The efferent arterioles, however, are spared (plate 218) in contrast to those of diabetic glomerulosclerosis The afferent arteriolosclerosis in amyloidosis, diabetic glomerulosclerosis, and benign nephrosclerosis generally has a smoother, more homogeneous, less granular quality than in malignant nephrosclerosis Occasionally whole glomeruli appear to be infarcted (plates 213, 214) Not infrequently, some of the glomeruli show the proliferative changes of acute glomerulitis even with the formation of capsular crescents identical with those of subacute glomerulonephritis (plate 218A) These glomerular changes are ischemic in origin The stroma of the cortex is often focally infiltrated with polymorphonuclear leukocytes Stromal extravasations of blood, corresponding to the "flea-bite" hemorrhages observed grossly, are frequent findings To repeat, additional histologic changes vary with the nature of the underlying renal disease




FIG A *Necrotizing afferent arteriolitis* of accelerated nephrosclerosis characterized by smudgy fibrinoid alteration of the wall, endothelial swelling, karyorrhexis of fibroblasts and inflammatory cells, and narrowing of the lumen

FIG B *Afferent arteriolitis* of accelerated (malignant) nephrosclerosis with characteristically extreme narrowing of lumen, concentric increase of intimal fibroblasts, necrobiosis of inflammatory cells and fibrinoid necrosis

FIG C *Typical lamination,* intimal cellularity, and luminal narrowing of accelerated afferent arteriolosclerosis This picture even without the necrosis indicates the accelerated hypertension

FIG D *Hemorrhage* within walls of necrotic afferent arterioles

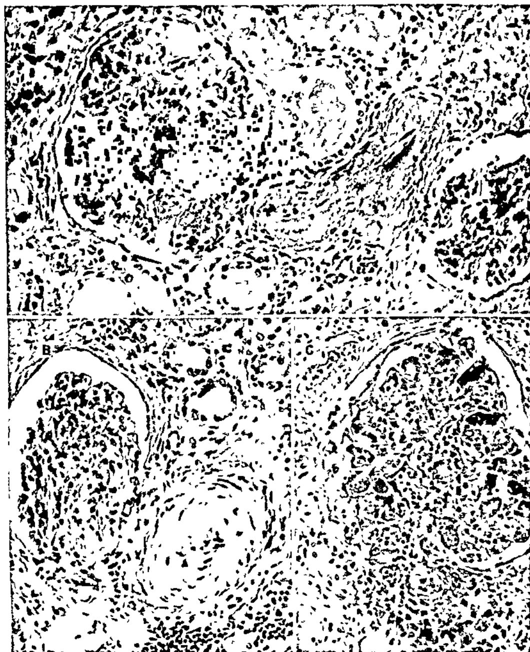



FIG A *Necrotizing afferent arteriolitis and glomerulitis* of accelerated (malignant) nephrosclerosis The glomerular hyalinization must be differentiated particularly from diabetic glomerulosclerosis and endocarditic glomerulonephritis

FIG B *Variant of afferent arteriolosclerosis* with marked edematous narrowing of lumen but without fibrinoid necrosis in accelerated nephrosclerosis

FIG C *Glomerulitis* of accelerated nephrosclerosis showing numerous thrombi in glomerular capillaries This lesion is not to be confused with that of disseminated lupus erythematosus Necrotizing arteriolitis is also present




FIG A *Typical smudgy fibrinoid swelling* with extreme narrowing of lumen of afferent arteriole in accelerated nephrosclerosis The associated proliferative glomerulitis is secondary to the ischemia This patient was a 34 year old white man with a blood pressure of $\frac{180\text{–}230}{90\text{–}120}$ (A F I P. Acc 106542)

FIG. C *Dilatation of necrotic afferent arteriole* is common in accelerated nephrosclerosis and has been thought to reflect increased intraglomerular tension

FIG. B *Fibrinoid necrosis and coalescence of capillary loops* of glomerular tuft in accelerated nephrosclerosis

FIG D. *Capillary thrombi and mild fibrinoid necrosis* of capillaries constitute one of the less striking glomerular changes of accelerated nephrosclerosis. This change also occurs in acute glomerulonephritis

present prior to the superimposition of the malignant phase.

Alterations may occur in organs other than the kidney in cases of malignant nephrosclerosis. The vessels of the retina are practically always involved in hypertensive retinopathy. Arteriolar necrosis may be found in the testis, pancreas, adrenal gland, gallbladder and liver. In some of these organs, for example the pancreas, a characteristic parenchymal atrophy may occur (Schurmann and MacMahon). Of course, in view of the frequency with which patients with malignant nephrosclerosis develop uremia, the extrarenal changes, previously described in the section on Uremia, may also be found in such patients.

*Pathogenesis*

The prominent position of hypertension in the list of leading causes of death has prompted a great expenditure of effort in search of the cause of this disease. This effort received enormous impetus with the discovery by Goldblatt and his associates (1934) of a relatively simple and constantly effective method for the experimental production of hypertension by means of constriction of the renal arteries with silver clamps. During the next decade, and especially the first half of that decade, immediately following Goldblatt's discovery, the natural ramifications of the problem were explored, a few modifications of the experimental methods were introduced, and several new concepts of the pathogenesis of hypertension were added. To date, no single concept is entirely adequate, no satisfactory therapeutic agent or procedure is available.

Many theories have been proposed to explain the pathogenesis of hypertension. The common occurrence of renal arterial and arteriolar sclerosis has strongly suggested that renal ischemia is a main pathogenetic factor. Some investigators blame excess of circulating pressor substances, insufficiency of antipressor hormones, the adrenal glands, the pituitary gland, diet especially with high protein, purine or sodium components, obesity, psychogenic stress, or abnormality of a vasomotor center.

Clearly, many of the hypotheses built about these general headings are simply complementary facets of an over-all mechanism. For example, a concept of neural genesis of hypertension need not preclude humoral, endocrinologic contributions; similarly, the notion that renal ischemia or renal vasoconstriction is responsible for hypertension does not necessarily imply that no other broad accessory factors are set into operation.

*Conclusions from experimental data*

An examination of the experimental facts indicates that the following are pertinent phenomena with regard to the production of hypertension:

1. Hypertension, both systolic and diastolic, sustained for years, can be produced in dogs by constriction of both main renal arteries, the silver clamps of Goldblatt are generally used for this purpose. This hypertension need *not* be accompanied by renal dysfunction.

2. Transient hypertension is produced in most dogs if the clamp is applied to only one main renal artery, chronic hypertension occurs in some dogs and in other animals such as rats, sheep and goats with constriction of one main renal artery. Sustained hypertension may be produced in most dogs by clamping one main renal artery, provided the contralateral kidney is removed as if this kidney, left intact, neutralized the pressor substance released by its vasoconstricted fellow. Sustained hypertension may be produced also by clamping the aorta proximal but not distal to the origin of the renal arteries, clamping of the celiac axis, the superior or inferior mesenteric arteries, the splenic or femoral arteries does not yield hypertension.

3. Release of the vasoconstricting clamp is followed by a return of the blood pressure to normal levels in a matter of hours.

4. Simultaneous occlusion of the main renal veins along with the constriction of the arteries does not result in hypertension. Moreover, oc-

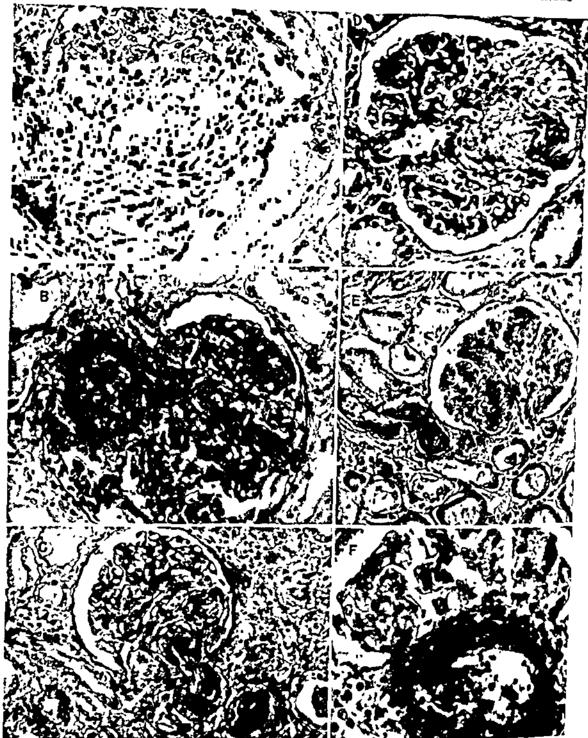



FIG A *Proliferative glomerulitis* of accelerated nephrosclerosis provoked by ischemia and simulating the changes of glomerulonephritis

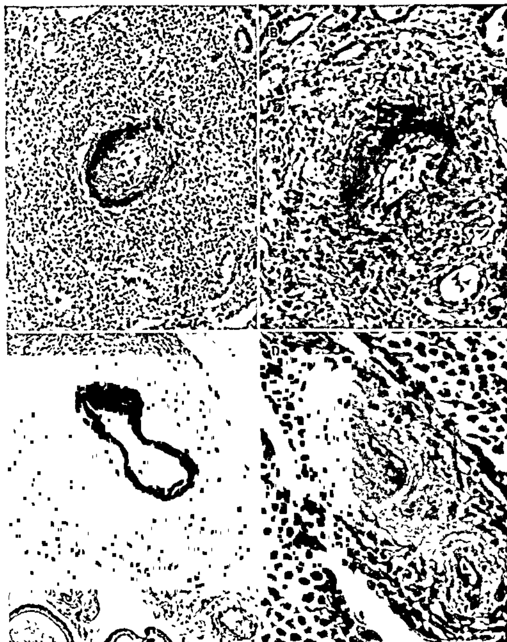
FIG B *Glomerulus of accelerated nephrosclerosis* showing marked necrosis of afferent arteriole with no change in efferent arteriole

FIG C *Accelerated nephrosclerosis* with necrotizing arteriolitis and organically negative efferent arteriole

FIG D *Glomerulus showing fibrinoid necrosis* of accelerated nephrosclerosis and torpid glomerular fibrosis of benign nephrosclerosis.

FIG E *Accelerated nephrosclerosis* with necrotizing afferent arteriolitis *and no change in the efferent arteriole.*

FIG F *Necrotizing afferent arteriolitis* with marked dilatation




FIGS A AND B *Necrotizing arteritis* (interlobular) of kidney of periarteritis nodosa, to be differentiated from arteritis of accelerated nephrosclerosis The abundant inflammatory reaction in these instances is strong presumptive evidence in favor of periarteritis or mycotic arteritis versus the arteritis of malignant nephrosclerosis Rarely do renal arteries exhibit such inflammatory response as a result of malignant hypertension

FIGS C AND D *Necrotizing arteritis* of testis of rat following severe hypertension produced by cellophane perinephritis

## PLATE 220. Glomerulonephritis with Accelerated (Malignant) Nephrosclerosis




Fig A *Subacute glomerulonephritis* with necrotizing afferent arteriolitis in a patient with the clinical picture of accelerated (malignant) nephrosclerosis Even though found with subacute glomerulonephritis, this arteriolitis is an indication of severe hypertension

Fig B *Chronic sclerosing glomerulonephritis* with superimposed accelerated (malignant) nephrosclerosis The laminated, markedly narrowed sections of artery represent a histologic indication of severe hypertension In other words, the accelerated (malignant) phase may complicate glomerulonephritis as well as benign nephrosclerosis and other conditions associated with an elevated blood pressure.

## PLATE 221 Accelerated (Malignant) Nephrosclerosis Superimposed on Glomerulonephritis

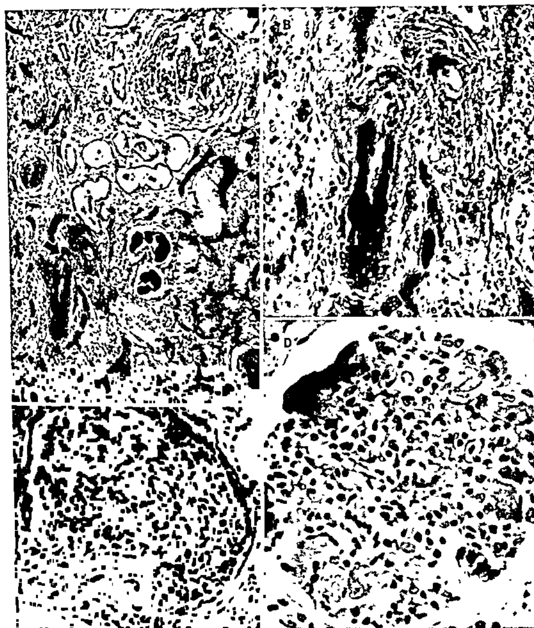


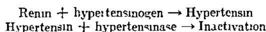

Fig A *Chronic sclerosing glomerulonephritis* with clinically and histologically superimposed accelerated nephrosclerosis

Fig C *Necrotizing afferent arteriolitis* of chronic glomerulonephritis with superimposed clinical and histologic accelerated nephrosclerosis

Fig B *Higher magnification of necrotizing interlobular arteritis* pictured in figure A

Fig D *Acute exudative glomerulonephritis* with thrombosis simulating accelerated (malignant) nephrosclerosis This glomerular lesion is not of itself indicative of hypertension

clusion of the renal veins after hypertension has been produced by clamping of the renal artery is followed by reduction of the pressure to normal (Goldblatt, 1947). The indication of this experiment is that constriction of the renal artery causes the release of a pressor substance to the general circulation and that this substance is withheld from the general circulation by closing the renal vein Injection of blood from the renal vein of an explanted kidney with a constricted artery into a normal animal results in hypertension, as if the pressor substance were humoral To some observers, the pressor agents are vasoconstricting amines which lead to hypertension in patients whose kidneys fail to deaminize them (Bing and Zucker) Most investigators believe the pressor substance to be *angiotonin* or *hypertensin* This material is the product of *renin* (apparently a proteolytic enzyme liberated by the kidney) plus *renin* substrate, or *hypertensinogen* (a pseudoglobulin) (Houssay and Taquini) The tissue protein that destroys angiotonin or hypertensin is known as *hypertensinase* or *angiotonase* (Braun-Menéndez et al ), that is


Renin + hypertensinogen → Hypertensin
Hypertensin + hypertensinase → Inactivation

5 Hypertensive effects similar to those obtained by constricting the main renal arteries may be obtained by enveloping the kidneys in cellophane, silk, a fish-skin envelope, tantalum foil or gauze impregnated with collodion, usually, *but not in all cases, with the production* of a constricting perinephritis

6 Occlusion of a ureter and constriction of the ipsolateral main renal artery of a dog do not result in even transient significant elevation of blood pressure. This is to say that an altogether functionless kidney on one side does not cause hypertension

7 In animals in which hypertension has been produced by constriction of the main renal arteries, the blood pressure which may fall after a while, may be restored to hypertensive levels by further tightening of the arterial clamps The fall in blood pressure in these instances is attributed to the development of collateral circulation through the capsule and pedicle Use of this principle by means of splenorenopexy has been made in lowering blood pressures of dogs made hypertensive by constriction of the main renal arteries (Cerqua and Samaan) Separation of the kidney from the spleen results in restoration of the hypertension Splenorenopexy in man does not effect a reduction of hypertension, a discrepancy which suggests to Victor that the mechanisms producing hypertension are different for man and dog

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FIG A *Chronic membranous glomerulonephritis from a 6 year old with associated malignant hyper*

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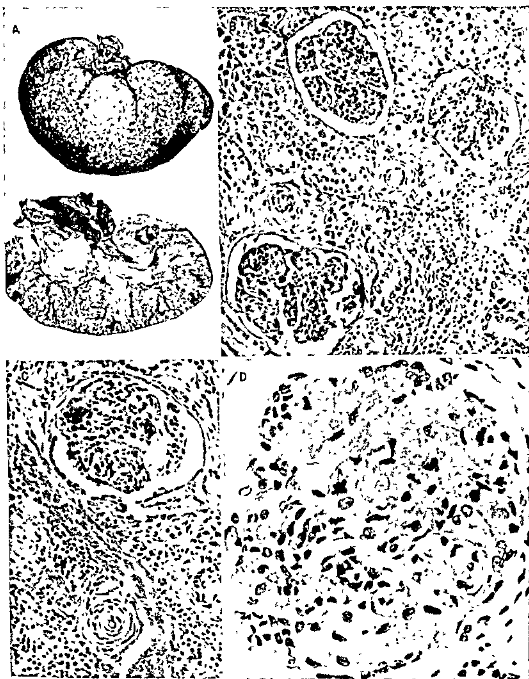
nephrosclerosis *The patient initially had the nephrotic syndrome*

FIG C *Chronic membranous glomerulonephritis* from kidney of figure A The cellular, fibrillar interlobular artery reflects the acceleration of malignant nephrosclerosis

FIG B *Chronic membranous glomerulonephritis with acceleration* Section taken from kidneys illustrated in figure A The glomerular change is of the combination lobular and membranous type

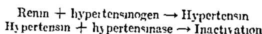
FIG D *Glomerulus of malignant nephrosclerosis* with fibrinoid necrosis of its capillaries, taken from kidney of figure A The few intact capillary walls show thickening of the membranous type associated *with the nephrotic complex*

PLATE 222 Chronic Membranous Glomerulonephritis with Superimposed Malignant Nephrosclerosis in a Child




(Legends on facing page )

clusion of the renal veins after hypertension has been produced by clamping of the renal artery is followed by reduction of the pressure to normal (Goldblatt, 1947) The indication of this experiment is that constriction of the renal artery causes the release of a pressor substance to the general circulation and that this substance is withheld from the general circulation by closing the renal vein Injection of blood from the renal vein of an explanted kidney with a constricted artery into a normal animal results in hypertension, as if the pressor substance were humoral To some observers, the pressor agents are vasoconstricting amines which lead to hypertension in patients whose kidneys fail to deaminize them (Bing and Zucker) Most investigators believe the pressor substance to be *angiotonin* or *hypertensin* This material is the product of *renin* (apparently a proteolytic enzyme liberated by the kidney) plus renin substrate, or *hypertensinogen* (a pseudoglobulin) (Houssay and Taquini) The tissue protein that destroys angiotonin or hypertensin is known as *hypertensinase* or *angiotonase* (Braun-Menéndez et al ), that is·


Renin + hypertensinogen → Hypertensin
Hypertensin + hypertensinase → Inactivation

5 Hypertensive effects similar to those obtained by constricting the main renal arteries may be obtained by enveloping the kidneys in cellophane, silk, a fish-skin envelope, tantalum foil or gauze impregnated with collodion, usually, but not in all cases, with the production of a constricting perinephritis.

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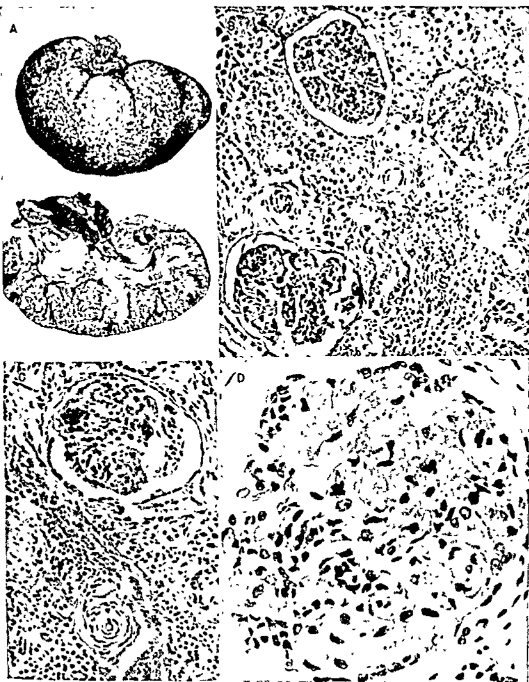
Fig A *Chronic membranous glomerulonephritis* from a 6 year old with associated malignant hypertension The surface granularity and scattered petechiae give these kidneys a remarkable picture identical with that of the adult kidneys with malignant nephrosclerosis The patient initially had the nephrotic syndrome

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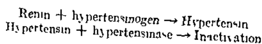
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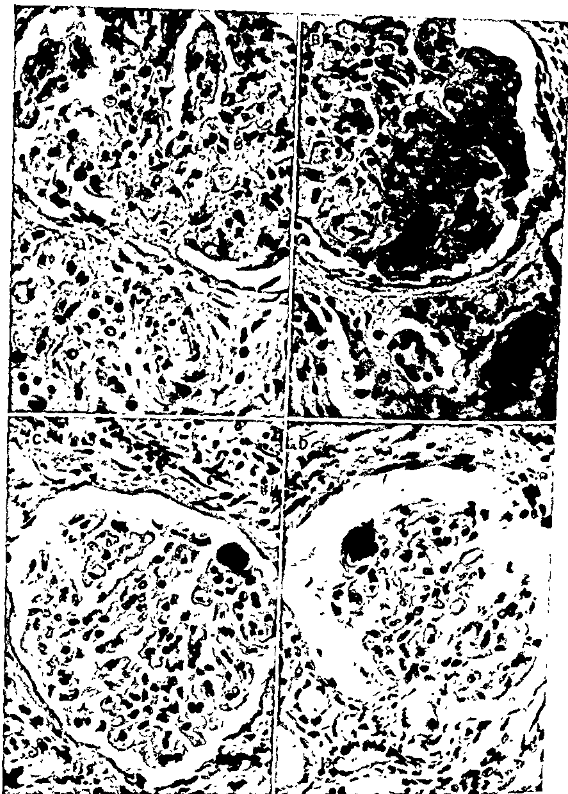
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PLATE 222. Chronic Membranous Glomerulonephritis with Superimposed Malignant Nephrosclerosis in a Child




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PLATE 223. CHRONIC MEMBRANOUS GLOMERULONEPHRITIS AND SUPERIMPOSED MALIGNANT NEPHROSCLEROSIS




FIGS A AND B *Chronic nephrotic glomerulonephritis with superimposed accelerated or malignant nephrosclerosis;* the accelerated phase is demonstrated by the partially necrotic afferent arterioles (arrow) and glomeruli (From kidney illustrated in figure A, plate 222)

FIGS C AND D. *Chronic membranous nephrotic glomerulonephritis* with hypertension and focal "wire-loop" necrosis of isolated capillaries

## PLATE 224. Hypertension: Unilateral Chronic Pyelonephritis with Superimposed Accelerated (Malignant) Nephrosclerosis




Fig A *Markedly atrophic pyelonephritic kidney* removed surgically from a hypertensive patient with unilateral disease The lower kidney from another patient is included for contrast

Fig B *Tubular dilatation,* proteid casts and interstitial fibrosis from atrophic kidney of figure A

Fig C *Necrotizing arteriolitis* (arrow) of malignant hypertension (from pyelonephritic kidney of figure A)

lation but from the failure of the kidney to act on a substance normally in the circulation.

10 The adrenal cortex is necessary for the development of hypertension

11. There are conflicting data on the vascular changes in the unobstructed kidney of rats in which malignant hypertension has been produced by constriction of the main renal artery of the opposite kidney. According to Wilson and Byrom necrotizing arteriolitis develops in the kidney with the free renal artery because of intense vasospasm associated with increased intrarenal vascular pressure whereas in the opposite, clamped kidney, the vessels are normal as if protected by the obstruction within the more proximal main artery. Goldblatt (1947) is inclined to attribute the arteriolitis to accompanying renal insufficiency or possibly to spontaneous lesions antedating the experiment. Goldblatt's opinion that renal insufficiency is required for the production of necrotizing arteriolitis of malignant hypertension is a point of view not universally shared (e g., Page, Fishberg).

12 As in human hypertension, viscosity and volume of blood, cardiac rate and output, venous and circulation times play no part in experimental hypertension

13 *Constriction of the artery to the kidney* explanted to the groin or neck also results in hypertension so that an intact nerve supply is not essential for this phenomenon.

14. Sustained reduction in renal blood flow is not a constant prerequisite for the development of hypertension in dogs or humans, although such reduction in animals is the rule, as it is in cases of hypertension in humans when uremia is present. Reduction in blood flow is not accompanied by abnormal arteriovenous difference in oxygen. Constriction of the main renal artery also produces a diminished *renal* pulse pressure which many observers consider significant in the mechanism of hypertension.

15. Arteriosclerosis of the kidney is not produced as a result of experimental hypertension.

The absence of renal insufficiency or of more than minimal arteriolosclerosis in 50 per cent of biopsy specimens of the kidney in cases of hypertension can not be used convincingly as nullifying evidence against the concept of the renal origin of hypertension even if it does indicate that renal arteriolosclerosis is not essential This is especially the case if it is believed with Grollman that the hypertension occurs because *the kidney fails to produce its normal supply* of a humoral agent. It is trite but relevant to remark that dysfunction of an organ need not necessarily be accompanied by histologic change. The alternate theories of the renal origin of hypertension are that the kidney elaborates an excess of circulating pressor substance, or that the kidney fails to detoxify normally existing pressor compounds, such as pressor amines (Bing and Zucker) because of the insufficiency of oxidative deamination of amino acids. To Grollman, however, these generally accepted "pressor-antipressor" theories are irreconcilable *with the fact that hypertension* persists in the absence of renal tissue and that, therefore, the hypertension could not be caused by renal pressor substances

*Unilateral Renal Disease and Hypertension*

The occurrence of hypertension in patients with unilateral renal disease has been offered as additional evidence of the renal origin of hypertension in humans Such data must be tem-

FIGS A AND C *Cortical necrosis* of the kidney (figure A) Although supplied by normal main renal artery shown below in figure C, the histologic sections (plate 226) reveal evidence also of malignant nephrosclerosis The opposite kidney and renal artery are shown in figures B and D

FIGS B AND D. *Normal contralateral kidney* (figure B), despite the markedly sclerotic, recently thrombosed, main renal artery, *shown below in figure* D The histologic sections are illustrated in plate 226. The patient was a 52 year old man

These kidneys are from a case of hypertension with a superimposed malignant phase, and a ter- ... *with the thrombosed renal artery but of the one with* ... ie kidney with the occluded vessel ... *ney*" (Arch. Path *51:* 30–37, 1951).

## PLATE 225 Hypertension (Unilateral Renal Disease): Occlusion of Renal Artery with Contralateral Cortical Necrosis and Contralateral Arteriolosclerosis




(Legends on facing page.)

pered, however, with the fact that the blood pressure may be temporarily lowered quite non-specifically by a variety of operations not associated with the kidneys (Volini and Flaxman). Furthermore, in several large series of cases, the incidence was as high or higher in the control population as in those patients with unilateral renal disease: 22.8 per cent and 21.8 per cent respectively (Friedman, Moschkowitz and Marrus), 24 per cent and 27.5 per cent (Oppenheimer, Klemperer and Moschkowitz); 29.3 per cent and 29.0 per cent (Baggenstoss and Barker).

There are individual cases, nevertheless, in which the total evaluation of the evidence compels a pathogenetic linkage of the hypertensive state with the unilateral renal disease. The particularly impressive features of these cases are the occurrence of severe hypertension in infants or children, the presence of arteriolosclerosis in only one of the kidneys in some instances, and, above all, the sustained relief of hypertension following nephrectomy. These are factors that supersede the sphere of the statistical studies just cited. Examples are two of Butler's patients, aged 7 and 10 each, with unilateral chronic pyelonephritis and relief of hypertension after nephrectomy. The period of followup was limited in the report to 20 months and 3 months respectively. Another case is the 7 year old girl mentioned previously, whose hypertension of $\frac{170-225}{110-178}$ was reduced to normal levels within several months after removal of a pyelonephritic kidney, the hypertensive retinopathy also disappeared. The pressure has remained normal for at least five years, at the time of the last report (Kennedy and Barker). Another is a 5 year old boy with an ectopic pelvic kidney and a blood pressure of 155/105. After nephrectomy, the blood pressure remained within essentially normal limits for the following ten years.* At the end of 12 years of observation, his blood pressure was 132/80 and there was no evidence of cardiac enlargement (Burkland et al.). Gasul, Glasser and Grossman added nine cases from the literature to one of their own, the ages varying from 2½ to 12 years, in which the hypertension was relieved for at least a year after nephrectomy. Eight of these were examples of chronic pyelonephritis; one was a hydronephrotic and the last was an "ectopic" kidney.

Another remarkable case, illustrated in plates 225 and 226, was characterized by marked arteriosclerosis of the main renal artery with terminal thrombosis; the opposite renal artery was widely patent and without necrosis. The parenchymal vessels of the kidney with the sclerotic main renal artery were essentially normal, while those of the contralateral kidney with the patent main renal artery showed sclerosis of the arcuate, interlobar and afferent arterioles, characteristic of benign and malignant hypertension (Aronson and Sampson). A terminal cortical necrosis developed in this kidney, the parenchyma of the kidney with the thrombosed, sclerotic main renal artery was spared. Other instances have been reported of occlusion of one main renal artery with little or

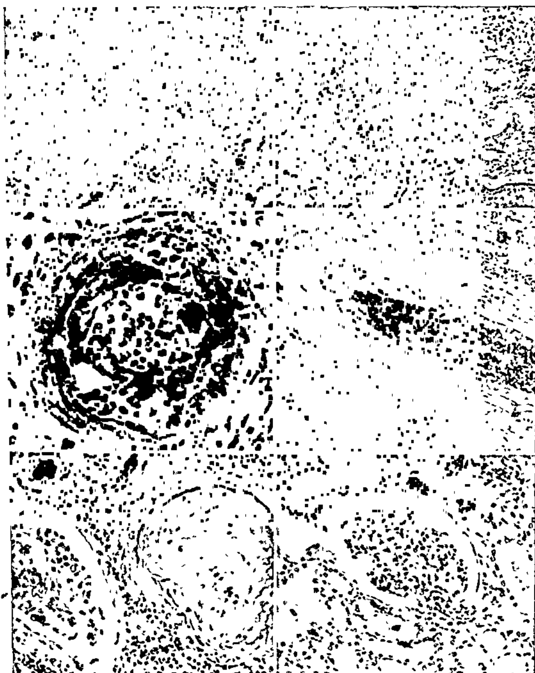
* The authors of this report (Burkland et al.) believe the main renal artery of the ectopic kidney was partially occluded by a "smooth muscle plug" with an elastic lamina. Actually, this "occlusion" appears to represent a well-known artefact produced by invagination of the wall of the artery (plate 339). This artefact, however, in no way invalidates the essential thesis of the report.

FIGS. A, B, AND C. Sections from the necrotic kidney of figure A, plate 225, showing the marked hyperplastic sclerosis of small arteries and arterioles (figures A and C), and the necrosis of an interlobular artery (figure B), indicating an associated malignant nephrosclerosis. The reason for the susceptibility of this one kidney to cortical necrosis is probably the pre-existing parenchymal sclerosis which made the kidney particularly vulnerable to a reduction in blood pressure. Thrombosis of the contralateral renal artery may have precipitated the altered hemodynamics by a reflex, or other neurogenic mechanism.

FIGS. D, E AND F. The parenchyma of the grossly normal kidney of figure B, plate 225, shows no significant histologic change despite the sclerosis and [illegible] The

effects of the hypertension. That this presumption does not always obtain is illustrated in plate 227.

PLATE 226. Hypertension: Occlusion of Renal Artery with Contralateral Cortical Necrosis and Contralateral Arteriolosclerosis



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# PLATE 227. Hypertension in Unilateral Renal Disease: Unilateral Thrombosis of Renal Artery with Ipsolateral Atrophy and Arteriolosclerosis

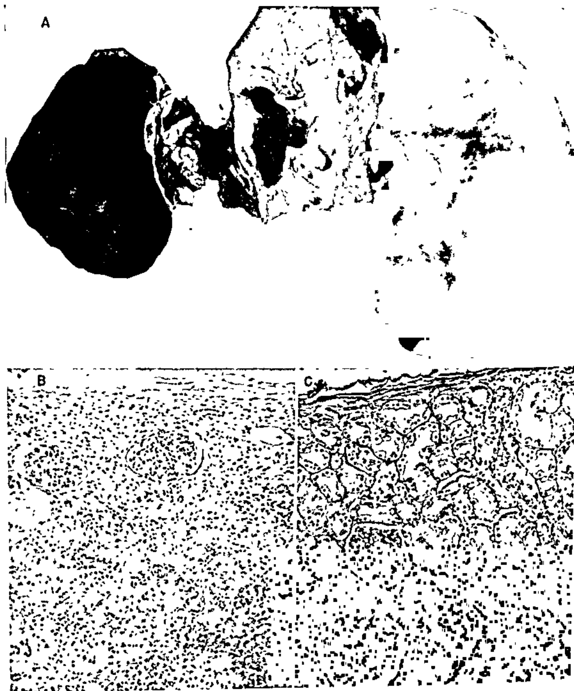
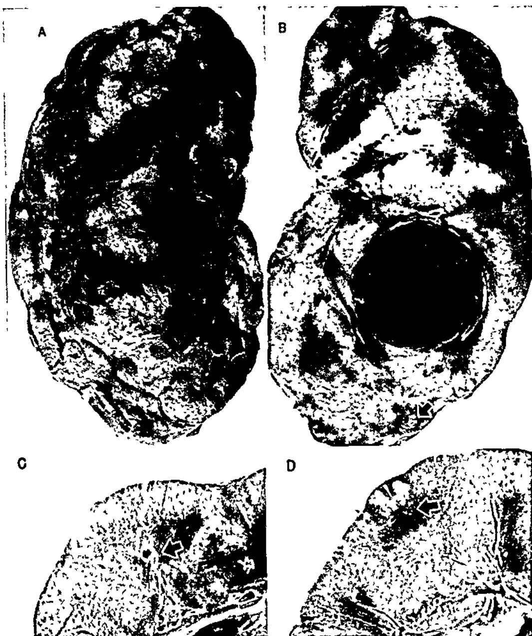



Fig A *Organized thrombus of left renal artery* with moderate atrophy of left kidney and associated hypertension The right kidney is of normal size and its artery is of normal caliber

Fig B *Section from left kidney* shown in figure A, showing evidence of tubular atrophy Arteriolosclerosis is present in contrast to the opposite kidney (C).

Fig C *Section from right kidney* in above figure A, showing an essentially normal histologic picture, including an absence of arteriolosclerosis The usual result in cases of unilateral occlusion of the renal artery is arteriolosclerosis of the contralateral kidney as in the case illustrated in plates 225 and 226




FIGS A AND B *Kidney with periarteritis nodosa* showing irregularly scarred capsular surface corresponding to ischemia produced by involvement of various sized arteries One of these arteries is aneurysmal in proportions and is filled with thrombus, others, such as the arcuate arteries (arrow) are extremely thickened and have narrowed lumens

FIG C *Periarteritis nodosa* An involved thrombosed arcuate artery is seen (arrow)

FIG D *Small renal infarct* and appertaining thrombosed arcuate artery are shown (arrow)

no changes in the parenchyma of the appertaining kidney, but with malignant nephrosclerosis in the opposite kidney of which the main renal artery was normal (Saphir and Ballenger, Schwartz and Gross)

There are definite exceptions to the rule that when the main renal artery is compromised, arteriolosclerosis occurs only in the contralateral, originally normal kidney. In the case shown in plate 225, the atrophic kidney with arteriolosclerosis is on the side of the occluded *main renal artery*, *in the opposite kidney*, the vessels are normal Hypertension was present In instances of unilateral *parenchymal* disease, as, for example, chronic pyelonephritis, the abnormal kidney is not protected from the occurrence of arteriolosclerosis This feature is illustrated in plate 224C in which malignant nephrosclerosis is shown superimposed on unilateral chronic pyelonephritis with marked renal atrophy

*Unilateral nephrectomy for hypertension*

In hypertensive cases with unilateral renal disease, either of the main renal artery or parenchyma, or both, the contralateral kidney is observed at autopsy to be altered usually by the vascular changes of benign nephrosclerosis, and occasionally, even of malignant nephrosclerosis. Many of the failures to relieve hypertension by unilateral nephrectomy of an abnormal kidney *are very likely based on the presence of arteriolosclerosis* produced in the opposite initially *normal kidney by the hypertensive state* In such instances, an earlier nephrectomy might have preceded the development of contralateral renal arteriolosclerosis which appears to sustain the hypertension after nephrectomy If the hypertension in a given case can reasonably be attributed to unilateral renal disease, it is clear that relief from nephrectomy cannot be anticipated unless the hypertension is discovered early. The exact definition of "early" is impossible to construct, but some idea of its range is derived from Braasch's observation that less than 1 per cent of patients with hypertension apparently secondary to unilateral renal disease are amenable to therapy for hypertension by nephrectomy Moreover, it must be borne in mind that the hypertensive state may occasionally be made worse by nephrectomy, depending particularly on the state of the retained kidney.

*Summary*

In summary, it would seem that most of the facts best fit a concept of the renal role in the genesis or mediation of essential hypertension As indicated previously, it would be dogmatically hazardous, and probably wrong, to dismiss the contributing factors of constitution, environmental stress, diet, endocrines, particularly the adrenal glands, and an inherent or acquired vulnerability of a vasomotor center or vascular bed to humoral stimuli.

## Periarteritis Nodosa

### *Introduction*

Kussmaul and Maier are credited with the first description of periarteritis nodosa in a patient clinically suspected of having trichinosis This report was published in 1866 and the clinical and pathologic (muscle biopsy) differentiation from trichinosis is often as much of a problem now as it was then. The pathogenetic role of hypersensitivity developed during the course of a prolonged infection was stressed by Gruber, convincingly reaffirmed by Spiegel, and subsequently effectively investigated by Rich with particular emphasis on the effects of the sulfonamides. The hypersensitive (hyperergic, allergic) concept of the nature of periarteritis nodosa is now generally accepted Supporting evidence for the allergic hypothesis from human material is derived from the eosinophilia in the peripheral blood and in the local lesions, the fibrinoid alteration in the vessels, and the common association with asthma and glomerulonephritis (Spiegel). Because of the increased opportunity for sensitization on account of the use of antibiotics, vaccines and sera in wholesale quantities, it is believed that the incidence of periarteritis nodosa has increased considerably in recent years

### *Clinical Symptoms*

The discordant array of signs and symptoms in itself is one of the characteristic features of periarteritis nodosa This is the natural result of the number of organs involved by this *usu-*

A

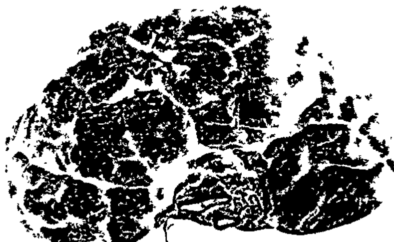
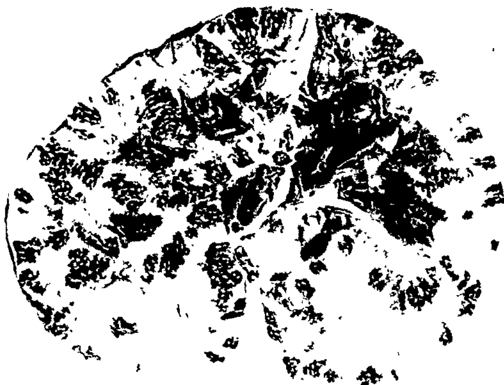




Fig A *Striking surface lobulation in periarteritis nodosa* due to diffuse involvement of renal arteries

Fig B *Periarteritis nodosa of kidney* showing thrombosis, aneurysmal dilatation and marked narrowing of arcuate artery by granulation tissue

A



B

FIG A *Multiple infarcts* due to periarteritis nodosa involving main branches of renal arteries and arcuate arteries This extensive degree of infarction produces a gross picture similar to that of bilateral cortical necrosis

FIG B *Cortical infarct* and thrombosis of interlobular artery in periarteritis nodosa

*ally* diffuse vascular disease. The process, however, selects certain organs above others and therefore symptoms pertaining to these structures predominate Polyneuritis, polymyositis, gastrointestinal symptoms, and evidence of renal damage are particularly common. In addition, signs of sepsis, acute cholecystitis, hepatic infarcts, acute pancreatitis, myocardial infarction, erythema, purpura, or subcutaneous nodules, serositis and severe hemorrhage may be present Eosinophilia is often observed, and may reach a level of 79 per cent (Strong)

### *Renal Involvement*

The kidney is the most commonly involved organ in cases of periarteritis nodosa (74 per cent, Gruber, 80 per cent, Arkin) The clinical evidence of renal involvement includes mild, moderate or malignant hypertension (17 of 30 cases, Ralston), renal insufficiency (33 per cent of cases, Ralston and Koale), hematuria, on occasion severe enough to cause death (Spiegel), perirenal mass (hematoma), and pain in the renal area An attempt to diagnose periarteritis nodosa by Addis counts has been reported by Krupp, who finds the sediment characteristic of all the stages of glomerulonephritis telescoped into one composite aggregate (page 172). This sediment, he states, is quite similar to that found in the urine in disseminated lupus erythematosus, notwithstanding their histologic differences. Inasmuch as these Addis counts are from a diversity of types of cases (periarteritis nodosa, disseminated lupus erythematosus) with at least an equal diversity of pathologic changes, it is difficult to understand the mechanism of the similar urinary sediments

### *Pathology*

#### *Gross appearance*

The kidneys with periarteritis nodosa may appear quite normal grossly When gross changes appear, they vary with the stage, extent and complications of the disease In the acute phase, the surfaces of the kidney may be mottled with hemorrhagic and yellow areas In later stages, highly irregular pittings and depressions from infarcts or areas of ischemic atrophy occur (plates 228, 229) In other words the kidneys may show the picture of malignant nephrosclerosis, acute glomerulonephritis, renal and perirenal hematomas, sometimes massive, and infarcts of different ages Renal infarcts were present in 35 of Gruber's 63 cases The infarcts may be so extensive as to simulate a complete cortical necrosis (plate 230 A) Usually the diagnosis is suggested by the examination of the vessels in the sectioned surface of the kidney. The cross sections of the arcuate arteries especially may be abnormally prominent, thickened and thrombosed, and the corresponding parenchyma may show the evidence of the ischemia (plate 230) Or, aneurysmal dilatation and thrombosis of even larger vessels, for example, the interlobar arteries, may be found Rupture of arteries (plate 228) may lead to massive intrarenal hemorrhage or perirenal hematomas. In addition, the kidneys in periarteritis nodosa may show evidence of benign or malignant nephrosclerosis, or acute diffuse glomerulonephritis

#### *Histologic appearance*

*Acute Stage* The lesions of periarteritis nodosa may be acute, healed, or recurrent Veins are rarely involved The *acute* stage is characterized by brightly acidophilic focal or massive fibrinoid degeneration of the arterial wall involving any or all of the coats and associated with little or with abundant inflammatory reaction (plate 229B, 231) The fibrinoid degeneration is stated to begin in the media, but it may begin in any portion of the vascular wall The initial localization is said to be dependent on the size of the vessel, but even in vessels of the same size, particularly of the arcuate arteries, the initial site of fibrinoid alteration may vary Often included in the area of fibrinoid necrosis are the elastic laminae, particularly the internal elastic lamina, and a portion of the media These structures are frequently disrupted as if by an extremely virulent, rapidly effected reaction so that the tough laminae may be torn into several fragments and displaced outward toward the adventitia This disruption, which is clearly shown in the Weigert's elastica-van Gieson stain, weakens the wall and is responsible for the subsequent aneurysmal nodosity (plate 232)

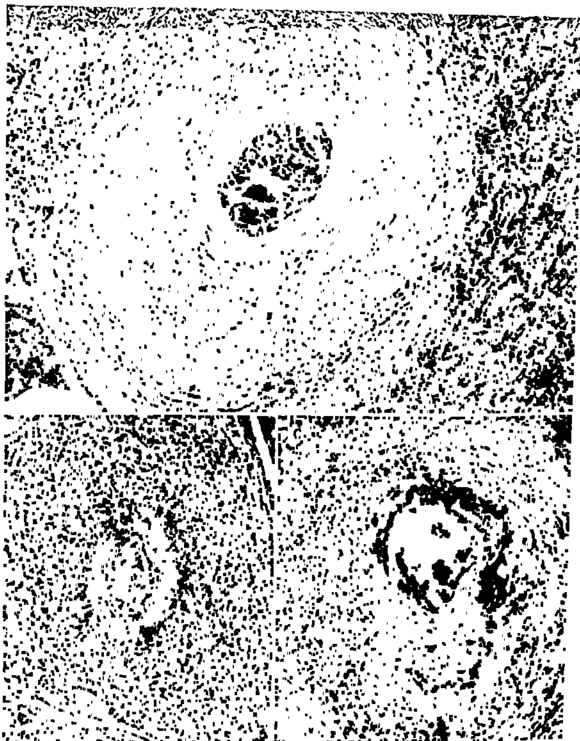


FIG A *Periarteritis of arcuate artery* with acute and chronic involvement of all coats of the vessel including the periadventitial tissue

FIG B *Fulminant exudative inflammation* and fibrinoid degeneration in periarteritis nodosa

FIG C. *Periarteritis nodosa* with smudgy fibrinoid degeneration and inflammatory reaction.



FIG A *Periarteritis nodosa (arcuate artery)* showing intimal sclerosis, disruption of the elastic lamina and aneurysmal dilatation responsible for the nodosity (Elastica–van Gieson stain)

FIG B *Disruption of elastica* and marked intimal sclerosis with extreme luminal narrowing of arcuate artery in "healed" periarteritis nodosa (Elastica–van Gieson stain)

The panarteritic inflammatory response typically consists of an abundant, diffusely distributed collection of eosinophilic leukocytes, polymorphonuclear leukocytes, lymphocytes, plasma cells and histiocytes In the past, the presence of eosinophilic leukocytes has been regarded as one of the essentials for the diagnosis of periarteritis nodosa This criterion has proved too rigid although it was perhaps justified at the time because of the then current tendency to include extraneous forms of arteritis in this group In point of fact, periarteritis nodosa in the acute stage need not be characterized by eosinophilic leukocytes Thrombosis and periadventitial hemorrhage occur frequently at this stage In addition to the haphazard outpouring of inflammatory cells, the acute stage may appear as granulomas with giant cells forming a conspicuous element of the response This latter reaction was known before the use of the sulfonamides, but is now commonly related to their use

*Healed Stage* The acute exudative and alterative stage may progress to the healing stage in individual vessels Rarely only the healing or healed residue of acute periarteritis nodosa is found; usually some focus of acute arteritis is present along with the healed vessels. The intima and media become eccentrically thickened by banal, at first cellular and well-vascularized, then densely sclerotic granulation tissue with marked encroachment on the lumen of the vessel (plate 232) The granulation tissue may extend in nodular formation beyond the adventitia With longer survival, the cellular, vascularized granulation tissue becomes indifferently dense and relatively acellular Old foci of residual hemosiderin-filled macrophages in the media, adventitia or even in the periadventitial region may indicate the nature of the ashes, especially if elastic tissue stains still reveal a torn lamina As a matter of practical diagnostic clue, the mere presence of a minute eccentrically placed lumen in marked disproportion to the width of the wall of an intrarenal artery is strongly suggestive of an old process of periarteritis nodosa Combine these with a dense sclerosis of the wall, spots of hemosiderin, and disrupted laminae and the diagnosis can hardly be anything else with the possible exception of a bacterial arteritis. The impression is gained that, very much as in the case of acute exacerbation of chronic glomerulonephritis, in which fibrotic glomeruli may occasionally undergo fibrinoid degeneration (plate 82), so also in healed periarteritis nodosa, a scarred vessel may succumb to an acute fibrinoid exacerbation (plate 231C).

So much for the primary vascular change of periarteritis nodosa The acute diffuse glomerulonephritis that often accompanies periarteritis nodosa may be exudative, proliferative, or necrotizing, and is best regarded as a pathogenetically related, rather than a coincidental change of periarteritis nodosa It occurred in one-third of Gruber's 63 cases, and in 3 of Spiegel's 17 cases Arterial involvement need not be present in the kidneys with glomerulonephritis in patients with periarteritis nodosa, as witness the case of Helpern and Trubek. Secondary or superimposed changes may include those of malignant nephrosclerosis, infarcts in various stages and of various sizes, and a form of tubular alteration that characterizes the atrophy produced by slowly progressive ischemia of renal vessels about the caliber of the arcuate arteries This change is marked principally by moderate separation of the tubules by the increased interstitial fibrous tissue, and by a conversion of the cells of the proximal tubules, which come to resemble the epithelium of distal convoluted tubules (plate 234, 235) The cells lose their brush border and their acidophilic cytoplasmic granules, and become diminished in height. The glomeruli participate in the atrophy to a lesser degree.

### *Differential Diagnosis*

The differential histologic diagnosis of periarteritis nodosa includes mycotic (bacterial or rickettsial) arteritis, the arteritis of malignant nephrosclerosis, the arteritis of disseminated lupus erythematosus, giant cell arteritis, and thromboangiitis obliterans It may be impossible to differentiate a given vascular lesion, out of setting, in any of the above diseases from periarteritis nodosa Several associated features may be of help. These diagnostic clues are the demonstration of infecting organisms in a case of mycotic arteritis, the glomerular wire-loop

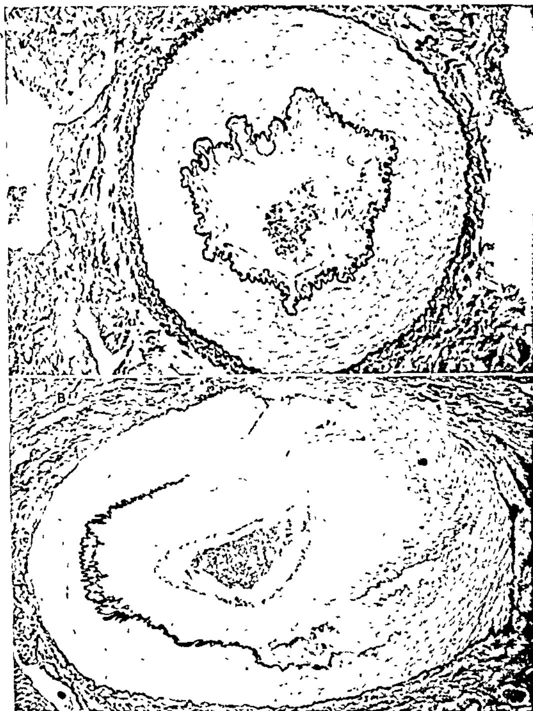



FIG A *Essentially normal arcuate artery* with elastica–van Gieson stain, in contrast to the vessels of periarteritis nodosa illustrated in plate 232

FIG B *"Disruption" of elastic lamina* in hyperplastic sclerosis without periarteritis nodosa No residual vascularized granulation tissue of periarteritis nodosa is present (elastica–van Gieson stain) Actually, the process in this section is not one of disruption, but of a loss of affinity for the stain The reduplicated elastic lamina can still be made out faintly




FIG A *Slow ischemic atrophy of proximal tubules* due to narrowing of arteries in periarteritis nodosa The glomeruli are spared The large segment of diffuse atrophy on the left is in contrast to the normal proximal tubules on the right The proximal tubules are the most sensitive to ischemic atrophy

FIG B *Diffuse chronic ischemic atrophy,* principally of the proximal tubules in periarteritis nodosa The glomeruli are relatively spared, rarely, focal endocarditic glomerulonephritis occurs

lesions of lupus erythematosus, and the characteristic evidence of accelerated arteriosclerosis and arteriolosclerosis of malignant hypertension, particularly in the smaller arteries and arterioles as against the usually larger ones of periarteritis nodosa In addition, in periarteritis nodosa, one looks for the absence of venous involvement, and, of course, the stigmata of periarteritis nodosa, especially the nodular healed lesions with minute lumens, organized thrombi, disrupted elastica, and hemosiderotic macrophages It should be emphasized again that diffuse visceral arteritis has, in the past, been taught to be the expected finding in disseminated lupus erythematosus and rickettsial diseases Nevertheless, as a matter of quantitative fact, it is uncommon in the kidneys of disseminated lupus erythematosus, and occurs infrequently and very sparsely in the kidneys of even epidemic and tick-borne typhus, it is practically never seen in scrub typhus If the appendix is excluded, periarteritis nodosa is uncommonly confined to one organ With regard to the isolated lesions of the appendix, there is some suggestion that the arteritis, discovered incidental to routine histologic examination, may not merit the ominous prognosis of periarteritis nodosa, despite the microscopic resemblance On the other hand, fatal periarteritis nodosa certainly may involve an appendix removed surgically (Spiegel), so that a blanket dismissal of these lesions is unwarranted at present

## Diabetic Glomerulosclerosis

### *Introduction*

Up until 1936, the only renal lesion more or less specifically associated with diabetes mellitus was the glycogenic vacuolization of the tubular epithelium of the loops of Henle In that year, attention was directed to an important contribution by Kimmelstiel and Wilson They described a form of glomerulosclerosis that tended to occur in diabetic patients with hypertension, retinopathy, albuminuria, hypoproteinemia and edema For a while this clinicopathologic association was treated with diffidence for several reasons First, those authors stated that the lesions were found "infrequently," an observation not subsequently borne out, but one which, at the time, probably discouraged interest somewhat. Second, they were of the erroneous impression that these peculiar globular lesions were merely histologically well advanced stages of the glomerular changes which they termed senile (arterial) nephrosclerosis Their identification of the diabetic glomerulosclerosis with simple senile nephrosclerosis diminished interest even further. Finally, it seemed unlikely to most casual observers that the significance of a distinctive glomerular lesion could have been badly missed for so many decades by the most astute renal investigators

Within five years, however, several reports appeared which, when pieced together, indicated that the clinical findings might indeed represent a genuine syndrome with a histologic counterpart, but there were two dissenting reports which are still difficult to explain In one of these (Horn and Smetana) it was stated that diabetic glomerulosclerosis occurred actually more commonly in nondiabetics than in diabetics, the other (Christian) concluded that the lesion was entirely nonspecific

In 1941 (Allen), the histologic lesion was defined in detail It was shown to be common in diabetic patients over the age of 40, to be practically specific for diabetes, to be a distinctive form of glomerular *capillary* sclerosis rather than an *intercapillary* sclerosis, and to be far and away the most reliable histologic criterion for the diagnosis of diabetes mellitus at postmortem Thereafter, a plethora of reports appeared over the next decade which appear to have confirmed the conclusions reached a decade ago Most of the details which follow are from the report published at that time and are still valid

### *Frequency of the Lesion*

The lesion occurs in approximately *one out of three diabetic patients over the age of 40* (Allen). Elsewhere, the reported incidence ranges from 20 per cent (Robbins) to 63 7 per cent (Laipply) for diabetic patients of all ages. Undoubtedly, the figure of 63 7 per cent can be explained by the inclusion of cases that do not meet all the histologic criteria That this is so




FIG A *Ischemic alteration* of the epithelium of the more vulnerable proximal tubules in periarteritis nodosa The cells of the altered proximal tubules come to resemble those of the distal tubules This histologic picture simulates the so-called "endocrine kidney" (of Selye) produced experimentally by partial occlusion of a renal artery with or without ureteral occlusion

FIG B *Cortical depression* following ischemic atrophy due to periarteritis nodosa The involved vessel and thrombus is at the right of the photograph

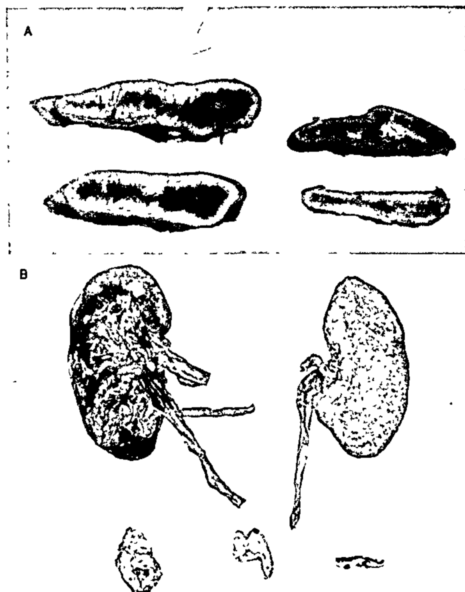



FIG A *Diffuse hyperplasia of adrenal glands* in association with periarteritis nodosa, hypertension and Cushing's syndrome The hyperplastic glands are at the left, normal adrenals are shown at the right for the contrast

FIG B *Periarteritis nodosa associated with hyperplasia of adrenal glands* Thrombosed vessels of periarteritis nodosa are visible in the adrenal glands at the bottom of the photograph

is indicated not only by two of their four photomicrographs but by their disputed finding of the lesion in 12.5 per cent of subacute and chronic glomerulonephritis.

### *Age and Sex Incidence*

In most series (Bell, Henderson et al ; Rifkin et al ; Siegel and Allen), there is a preponderance of females. The lesion occurs infrequently below the age of 40 Only one (aged 34) was found in our series (Siegel and Allen) and none in Bell's material below the age of 30, the youngest reported case to date is 16 years of age (Laippley et al.). We have reviewed many instances of chronic lobular *glomerulonephritis* (plate 245E) in young patients whose renal lesions have been mistaken for those of diabetic glomerulosclerosis.

### *Specificity of the Lesion of Diabetic Glomerulosclerosis*

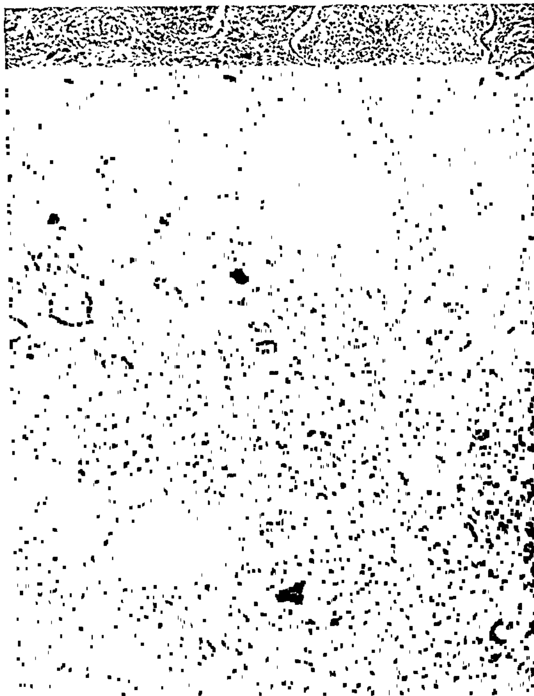
Much unfortunate confusion has resulted from the publication of data indicating the occurrence of the lesion of diabetic glomerulosclerosis in a remarkably large number of nondiabetic patients (Horn and Smetana, Henderson et al., Laippley et al.; Goodof) In one series (Goodof) the lesions were found in 30 per cent of nondiabetic patients over the age of 70. In contrast, we have found the lesion only once in a nondiabetic (on whom no glucose tolerance curve had been done) Bell also has seen the nodular lesion of diabetic glomerulosclerosis in only 2 one nondiabetic. At four large institutions [Memorial Hospital, New York, the Kingsbridge Veterans Hospital, the Army Institute of Pathology (1942–1946) and the Mallory Institute of Pathology (Robbins)], the lesion of diabetic glomerulosclerosis has not been found in a single nondiabetic patient Therefore, it appears reasonable to conclude that reports of nonspecificity are based principally on the inclusion of extraneous lesions in the group. Another possible source of misinterpretation is the fact that diabetes in these elderly patients is usually mild, often requiring no insulin for control, and the renal threshold for glycosuria may be elevated (Mirsky and Nelson). Hence, the elimination of the diagnosis of diabetes mellitus merely on the absence of glycosuria unjustifiably masks a number of cases.

In conclusion, then, the characteristic nodular lesion of *diabetic glomerulosclerosis* may be considered specific for all practical purposes. This conclusion is further supported by the experimental production of the lesion in diabetic animals (Lukens and Dohan).

### *Clinical Picture*

Diabetic glomerulosclerosis may occur without any symptoms related thereto In such cases, it may be assumed that the lesions are sparse, involving only a few scattered glomeruli If the lesions are numerous and are present in practically all of the glomeruli (grade 4 + on a scale 1 + to 4 +), it may then be assumed, with great odds, that the entire clinical complex of diabetes, hypertension and the nephrotic syndrome is present Conversely, if the patient presents himself with the full clinical picture, the likelihood of diabetic glomerulosclerosis being found is also great. However, because other renal lesions, such as amyloidosis and some forms of chronic glomerulonephritis, may also result in the nephrotic syndrome in a diabetic patient, these two possibilities must be taken into diagnostic account. Intermediate grades of severity of the clinical syndrome are generally associated with more or less corresponding degrees of diabetic glomerulosclerosis (Siegel and Allen).

As stated, the diabetes is usually mild, often requiring little or no insulin for control. The diabetes apparently precedes the development of the lesions from 3 to 20 years or more (Siegel and Allen). We have seen one diabetic patient in whom the lesions were present in the one kidney at autopsy but were absent in the kidney removed surgically three years previously. This case parallels that of Derow, Altschule, and Schlesinger in which the lesions appeared to take four years to develop Hypertension and hypertensive retinopathy are almost constant when diabetic glomerulosclerosis is widespread Azotemia, at times associated with myocardial failure occurs in about 75 per cent of cases of severe diabetic glomerulosclerosis and frequently progresses to uremia. Hypoproteinemia with reversal of the albumin-globulin ratio,




FIGS. A AND B *Granulomatous giant cell arteritis* of arcuate and interlobar arteries, considered to represent an allergic reaction akin to periarteritis nodosa Similar reactions have been attributed to sulfonamides, none was used in this case

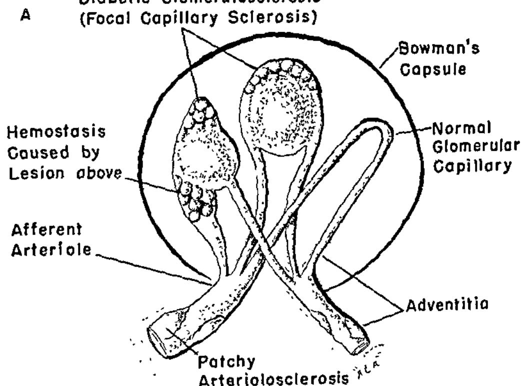









FIG A *The origin from the capillary wall* of the lesion of diabetic glomerulosclerosis is diagrammatically illustrated The capillary bulge causes a stenosis of the capillary lumen as well as marked dilatation

FIG B *The kidney with diabetic glomerulosclerosis* usually is of normal or greater than normal size and has the stigmata of arterial and arteriolar nephrosclerosis

FIG C *Thin unusually dilated capillaries and lamination of endothelial cells and fibers* are characteristic of the periphery of the hyaline masses of diabetic glomerulosclerosis

and hypercholesterolemia is common and appears to be related to the albuminuria. Of course a fraction of the hypercholesterolemia may be an intrinsic part of the diabetes mellitus and independent of the nephrotic syndrome.

### *Prognosis*

With the development of the complete renal component of the syndrome, the prognosis becomes grave and life expectancy is about two to three years. Death is likely to result from uremia and/or cardiac failure.

### *Pathology*

*Gross appearance*

Not only are the kidneys with diabetic glomerulosclerosis not contracted, but they are likely to be slightly to moderately larger than normal (plate 238B). Such enlargement is characteristic of kidneys from patients with the clinical nephrotic syndrome (albuminuria, hypoproteinemia, reversal of albumin-globulin ratio, edema and hypercholesterolemia) from other causes such as amyloidosis, and chronic membranous or lobular glomerulonephritis.

*Histologic appearance* (plates 238 to 247)

The lesions in the kidneys may be diffuse or sparse. They may involve practically all of the glomeruli in a section or merely one, and this isolated lesion may be quite as typical as those in the more extensively affected kidneys. They characteristically show much variability in size, ranging from approximately 20 microns to about 120 microns in their greatest diameter. Hence, a large lesion may occupy more than a third of the volume of a glomerulus. The lesions are generally more or less spherical although occasional oval ones are seen, with the longer diameter two or three times the other. There is a tendency for the initial lesion or the largest lesion to be opposite, rather than adjacent, to the vascular pole of the glomerulus (plate 241B). The involved glomeruli, in spite of the hyalinization, need not be small, they may be as large or frequently larger than normal. In small glomeruli the hyaline mass may bulge the portion of Bowman's capsule immediately about it. Bowman's space may be of normal width, not infrequently, however, it is widened and may be filled with protein and lipid precipitate.

The typical lesion consists of hyalinized acidophilic material, which with low magnification appears almost completely homogeneous. With greater magnification, there is a circumferentially laminated structure, often pitted with a few small vacuoles (plate 239C). The fibrillated hyalin is dull and dense appearing, manifesting little or none of the refractility of the "wire-loops" seen in the glomeruli of acute disseminated lupus erythematosus. The acidophilia of the lesions, as a rule, is not quite as marked as that of the walls of the appertaining arterioles. The hyalin does not react positively with stains for amyloid or fat.

The cellularity of the lesions varies in quantity, disposition and character. Often there are two or three peripheral concentric layers of flattened cells (plate 241A). These appear to be mostly displaced endothelial and occasional epithelial cells. The core is generally devoid of cells, although occasional vesicular or more or less pyknotic distorted nuclei, and even a red blood cell or two, may be found near the center (plate 241A). The impression that in some of the lesions there is an increase of cells results from a tangential section passing through the cellular rim at the periphery of the lesion (plate 241D). A few endothelial and epithelial foam cells are seen (plate 239C).

*Capillary vs. intercapillary origin*

Reconstruction of the lesion from serial sections reveals that *it is not an intercapillary mass* or bar of hyalin which extends from the hilar arterioles to the periphery of the glomerulus, as Kimmelstiel and Wilson have believed. Rather, it is a mass of hyalin formed by an abrupt thickening of the wall of one or more closely situated capillaries, with resultant encroachment on and often obliteration of their lumens (Allen). These lumens are almost invariably obliterated in sections through the "equator" of the mass or through its great arcs, but near the poles of the globes, that is, as one approaches tangential sections, lumens containing red blood cells and lined by endothelium become apparent (plate 239C). In kidneys with widespread lesions, there may be observed in a




FIGS A AND B *Diabetic glomerulosclerosis* showing bland afferent arteriolosclerosis and evolutionary stages of glomerulosclerosis, indicating the origin of the lesions from sclerosis of capillary walls rather than from "intercapillary" tissue Note that the capillary lumens are still unobliterated by the sclerotic walls of the incomplete lesion

FIG C *Diabetic glomerulosclerosis* clearly originating from sclerosis of capillary walls rather than from so-called intercapillary mesangium Endothelial cells are vacuolated by lipid.




FIG A *The lesion of diabetic glomerulosclerosis* is essentially free of fat, as here shown The lipid (black) is in endothelial and epithelial cells, in Bowman's capsule and focally in the afferent arterioles (Sudan III stain) Anisotropic fat occurs in the proximal convoluted tubules not only with diabetic glomerulosclerosis but with amyloidosis (figure C) and other conditions associated with the nephrotic syndrome

FIG B *Diabetic glomerulosclerosis* showing that the hyalinized glomerular lesion is free of fat (black) which is present in Bowman's space and capsule (Sudan III stain)

FIG C *Amyloidosis of glomerulus* which simulates diabetic glomerulosclerosis There is also lipid vacuolization of the proximal convoluted tubules This combined picture indicates that the patient had the clinical nephrotic syndrome

single section of a glomerulus the crude equivalent of serial sections, in the form of a variety of transitional phases of the multiple lesions in different parts of the tuft (plate 239A) In such glomeruli there may be normal capillary loops, loops of which only a crescentic segment has undergone the characteristic hyalinization, loops of which the entire wall has become hyalinized so as to leave only a narrow lumen containing one or two red blood cells, and, finally, the typical hyaline disc in which the lumen has been obliterated.

*Glomerular permeability*

A characteristic and, physiologically, probably important component of the lesion is dilatation of the capillaries situated at the rim of the lesion Immediately external to the hyaline mass, the capillary walls are thinned, lobulated and practically constantly dilated at some level of their course as observed in serial sections Commonly there is a single capillary loop partially or completely circumscribed about a large diabetic lesion Even though the space between the centrally placed disc and the external wall of such capillaries may appear deceptively small, it is obvious that these capillaries, encircling, as they do, the large hyaline mass, are greatly dilated (plate 242A) These peripheral capillaries may be jammed solid with red blood cells, or they may contain laked blood and much protein precipitate, some of which may have escaped into Bowman's space. The most strikingly dilated loops may contain small clots composed of a delicate fibrin mesh and platelets. The walls of these distended capillaries have escaped thickening and have been stretched excessively, as if the diabetic lesion had caused a stenosis of the capillary lumen with consequent proximal dilatation (plate 238A). The possible physiologic significance of this finding will be discussed

Of course, in the same section, there are, in addition, glomeruli which exhibit the changes characteristic of ordinary nephrosclerosis. These changes may be present in the very same glomeruli involved by the diabetic lesion and may be easily distinguishable from the latter. The simple nephrosclerotic portions of the glomeruli are differentiated by several criteria, chief among which is the feature that no one capillary loop appreciably outstrips its neighbor in degree of hyalinization. This holds even in the most advanced cases of nephrosclerosis and is in contrast to the typically focal hyalinization in the diabetic kidney (plate 245).

*Special stains*: With the Mallory-Heidenhain stain, the diabetic lesions are the deep blue of collagen, as a rule, but incompletely collagenized foci stain pink or purple orange Although the crescentic foci of thickening of capillary walls of the *early* lesions are easily noted in routine sections, they are perhaps more clearly visualized with the special stains for collagen. The red blood cells within the lumen of an evolving lesion leave no doubt of its capillary rather than intercapillary genesis (plate 241A, [illegible]

those of the azocarmine stain.

The silver stain (Foot's modification of the Bielschowsky stain) is of particular help in the analysis of the lesion. Characteristically, the diabetic hyaline body which stains a more or less homogeneous pink with hematoxylin-eosin, is found to be composed of a mass of black or deep brown fibers, which are often laminated and are easily and sharply differentiated from the uninvolved portions of the glomerulus Even the crescentic mural capillary thickenings of the early or small lesions are revealed as laminations of argyrophilic or dense collagenous fibers (plate 243) The remarkable feature is the pronounced difference between the argyrophilia of the diabetic lesions and the relatively slight affinity, with the Bielschowsky stain, of the remaining capillary loops even within the same glomerulus, however atrophied this structure may be Some of the large lesions show argyrophilic fibers at the periphery while the core stains the golden or deep brown characteristic of collagen This brown coloration differs distinctly from the pink of the counter-stained, atrophied capillaries of the nonspecific sclerotic portions of the glomerulus. The hyalin of the diabetic lesion thus becomes distinguishable with a high degree of reliability from the hyalin of the simple nephrosclerotic lesion in the glomerulus It might be added that, in tinctorial

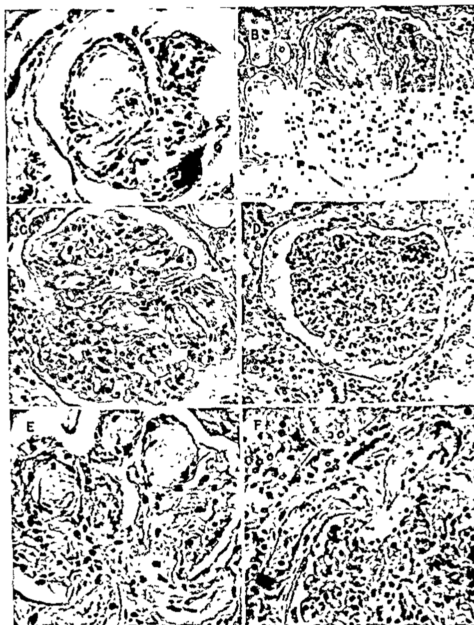



FIG A *Capillary origin* of diabetic glomerulosclerosis Red blood cells are present in the lumen of the incompletely formed lesion Hematuria is absent or mild

FIG B *The early lesion* of diabetic glomerulosclerosis is located characteristically opposite the vascular pole The laminated cells are seen at the periphery of the sphere

FIG C *Diabetic glomerulosclerosis* showing the origin from capillary walls The remainder of the tuft shows the picture of so-called diffuse glomerulosclerosis, of questionable diagnostic value by itself

FIG D *A cellular focus* as in the above photograph results from a tangential section through the cellular periphery of a lesion

FIGS E AND F *Efferent as well as afferent arteriolosclerosis* in diabetic glomerulosclerosis Efferent arteriolosclerosis is common in advanced diabetic glomerulosclerosis and rare, or absent, in other diseases of the kidney

properties, the hyalin of the diabetic lesions differs too from that found in the ovarian, uterine and splenic vessels and from the hyalin present in the islets of Langerhans (plate 243D). The unmistakable contrast between the scanty argyrophilia of the pancreatic islets and the abundant argyrophilia of the glomerular lesions in diabetes clearly and significantly differentiates the two types of hyalin Moreover, the hyalin of the islets also stains (if inconstantly) with metachromatic stains for amyloid.

*Fat stains*

There is commonly a moderate amount of fat, chiefly neutral but some anisotropic, located principally in the proximal convoluted tubules and in arterioles and interlobular arteries. Crescentic deposits of sudanophilic material are also found in Bowman's space (plate 240A). A few fat droplets are dispersed in endothelial and epithelial cells within glomeruli. The diabetic lesion itself usually contains no fat or just scattered minute droplets The diagnostic value of birefringent lipiduria has recently been emphasized (Rifkin et al ) However, birefringent lipids may be found in the urine in all varieties of disease with the clinical nephrotic syndrome including diabetic glomerulosclerosis, amyloidosis and chronic nephrotic glomerulonephritis. Nevertheless, the finding of anisotropic fat may be of help in distinguishing renal from extrarenal edema.

*Glycogen*

The Armanni-Ebstein or glycogen vacuoles in the loops of Henle are rarely found This is hardly surprising inasmuch as these vacuoles are commonly associated with severe, uncontrolled cases of diabetes mellitus

*Tryptic digestion*

In an attempt to define further the particular type of hyalin in these kidneys and to distinguish the hyalin of the diabetic glomerular lesions from that of the arterioles, the digestibility with trypsin was determined The following are the observations made after digestion by trypsin for an average of 24 hours at 37°C. The solution was alkalinized with sodium carbonate and 1 cc of chloroform was added for its preservative action (Allen).

1 The diabetic lesion, as a rule, manifested marked resistance to trypsin This is in keeping with the frequent argyrophilia and dense collagenous composition of the lesions.

2. The remainder of the capillary loops, that is, those in the nonspecific sclerotic portions of the glomeruli, exhibit slight digestibility. This is demonstrated by the diminished affinity for aniline blue of these loops in sections exposed to trypsin, as contrasted with the undigested control slide with the diabetic lesions in the same section or even the very same glomerulus (plate 242C).

3. The thickened Bowman's capsule and the basement membrane of the tubules resist digestion These are argyrophilic

4. A contrast is offered by the digestibility of the hyalinized portions of the arterioles. This pertains principally to the central parts of the arteriolar walls, since the inner and outermost portions are often argyrophilic and hence indigestible

*Hyalin involvement of the arterioles*· There appears to be a practically constant association

FIG A *Cavernous dilatation of capillaries* at the periphery of a lesion of diabetic glomerulosclerosis This is a common phenomenon in various degrees about most lesions of diabetic glomerulosclerosis, but may require serial sections to detect (Goldner's modification of Masson's trichrome stain)

FIG D *Capillary sclerosis* as the morphologic basis of the lesion of diabetic glomerulosclerosis is detected in several of these incompletely developed lesions Red blood cells are actually in the lumens of the capillaries, the walls of which are focally thickened (arrow).

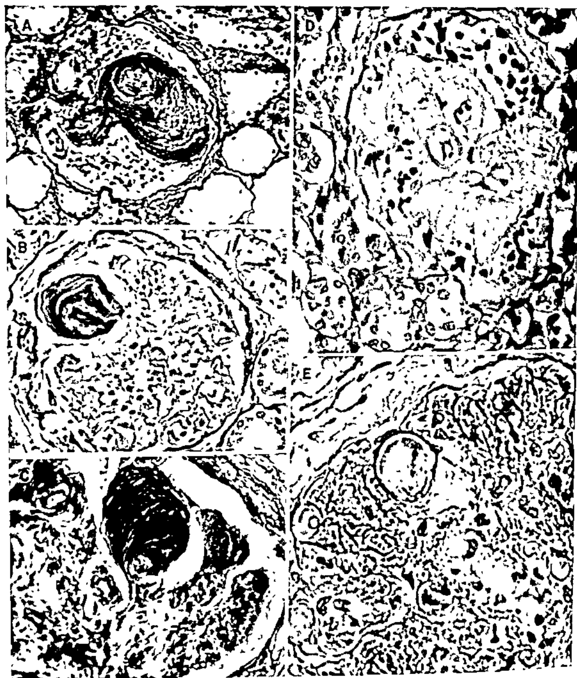
FIG B. *Peripheral dilatation* of thin walled capillary (arrows), many sites of mural origin of diabetic glomerulosclerosis are also shown

FIG C *Resistance to tryptic digestion* of lesion of diabetic glomerulosclerosis is demonstrated by obvious contrast with the remainder of the tuft (Tryptic digestion and Mallory-Heidenhain stain)

FIG E *Capillary origin* of diabetic glomerulosclerosis, formation of earliest lesions opposite the vascular pole and focal capillary sclerosis are demonstrated in this photograph




(Legends on facing page)




FIGS A, B, AND C *Laminated argyrophilia* is characteristic of the lesions of diabetic glomerulosclerosis There is a striking and fundamentally significant contrast in affinity for silver between the diabetic lesion and the remainder of the tuft made sclerotic by aging or benign nephrosclerosis (Bielschowsky's silver stain)

FIG D *Hyalin in the islets of Langerhans* of the pancreas is different in composition from that of diabetic glomerulosclerosis The argyrophilia of the islets is sparse and scattered (Modified Bielschowsky's silver stain)

[illegible] with

of diabetic glomerulosclerosis (Modified Bielscho[illegible]sky's silver stain)

of the diabetic lesion with afferent arteriolosclerosis Only rarely are lesions found in glomeruli whose afferent arterioles are thin walled. Occasionally the arterioles may appear normal in a single section, however, because of the uneven, in places, discontinuous thickening that may be present in these vessels (plate 240A), there may be found a markedly thickened segment elsewhere along their course if the sections are examined serially

A finding of considerable interest is the thickening and narrowing of the *efferent arterioles* by a hyaline material identical with that in the afferent arterioles The efferent vessels are, as a rule, not as strikingly thickened as the afferent ones, nor are they as constantly affected For example, in one of the more severely involved kidneys, only about a third of the efferent arterioles were thickened and narrowed as opposed to a practically constant involvement of the afferent arterioles

The hyalin of the arterioles differs in several respects from that of the diabetic glomerular lesions First, there is usually a much greater abundance of fat in the arteriolar walls (plate 240A) As a matter of fact, the fully collagenized diabetic lesions may contain no fat. Second, the arteriolar hyalin is generally more intensely eosinophilic In addition, there is frequently present a basophilic tint in the hyalin of the arterioles stained with hematoxylin-eosin, which is found in the midportions of the wall so as to correspond to a highlight This tint signifies a "soft" hyalin that is digestible with trypsin and does not take the stains for collagen Third, the arteriolar hyalin is typically bright red with the azocarmine stain, whereas the diabetic lesions are predominantly blue, indicating the collagenization of the latter Fourth, they lack the resistance to tryptic digestion so characteristic of the diabetic lesions (plate 242C). Finally, there is a distinct difference in the amount and distribution of the argyrophilic fibers in the two locations (plate 243) Similar though less marked changes may be seen in the afferent arterioles of nephrosclerotic kidneys from nondiabetic patients, with the absence, however, of the diabetic glomerular lesions. The prearteriolar interlobular arteries are also frequently thickened and narrowed by irregular hillocks of azocarminophilic hyalinized material.

*Vascular sclerosis vs lack of renal contraction*

There may be a remarkable disparity between the degree of vascular involvement, on the one hand, and the relative lack of gross renal contraction and granularity, on the other. This feature was noted by Kimmelstiel and Wilson, who felt that the "contraction may be in part or completely obscured by the signs of nephrosis." What this means in terms of actual histologic changes is not clear. Surprisingly enough, it is not a simple matter to account for the illusory smoothness and enlargement of the kidneys even from the sections themselves. To be sure, there usually are numerous areas of cortical atrophy (although this need not be marked even with extensive diabetic glomerular lesions) alternating with foci of dilated tubules, yet without the expected proportionate gross granularity and contraction Failing a micrometric examination, the only morphologic clue one gets is that the scar tissue is edematous and not as compact as in benign nephrosclerosis and that the tubular epithelium is focally swollen with fat.

## *Differential Histologic Diagnosis*

The lesions of diabetic glomerulosclerosis have been confused with (1) amyloidosis, (2) nonspecific glomerulosclerosis of any atrophic kidney, (3) chronic lobular (nephrotic) glomerulonephritis, (4) focal endocarditic glomerulonephritis and (5) "wire-loop" glomerulitis of disseminated lupus erythematosus.

*Amyloidosis*

In routine sections stained with hematoxylin and eosin, the hyalin of the glomerular amyloid is smoother, smudgier and as judged by the [illegible] marks, and the peripheral rows of nuclei of the diabetic lesion, are generally lacking in amyloidosis In addition, the amyloidosis, in contrast to the diabetic lesion, may also conspicuously involve the tubular basement membranes and arteries in a distinctive manner (plate 251B).

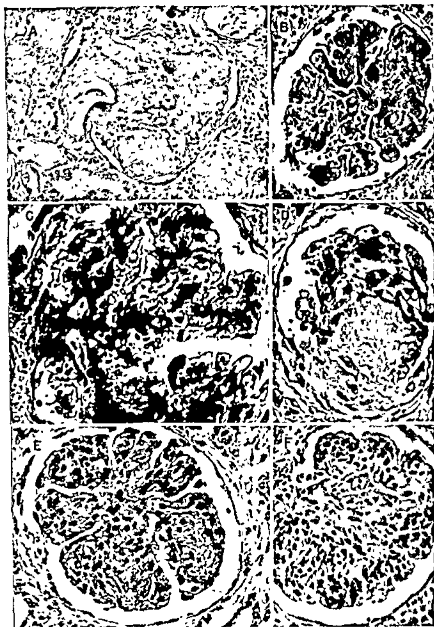



FIG A *Glomerular amyloidosis* The efferent arteriole is occasionally involved in amyloidosis

FIG B *Disseminated lupus erythematosus* with verrucal capillaritis due to exaggerated fibrinoid swelling

FIG C *Hypertensive glomerulus* of benign nephrosclerosis with capillary sclerosis (Elastica–van Gieson stain)

FIG D *Chronic sclerosing glomerulonephritis with focal sclerosis of the tuft*

FIG E *Chronic lobular glomerulonephritis* with characteristically uniform lobulation which involves all the glomeruli

FIG F *Chronic nephrotic glomerulonephritis* partially lobular and partially membranous

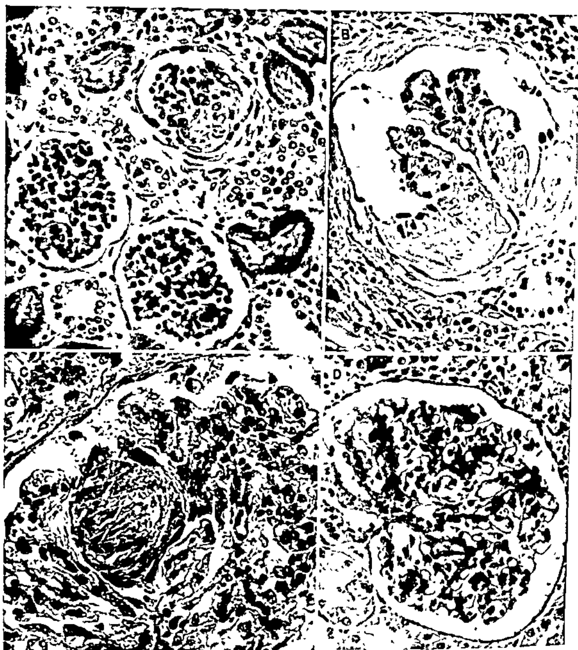



FIG. A *Congenital glomerulosclerosis*, an incidental finding in the kidney of an infant

FIG B *Sclerotic atrophy* of glomerulus in hydronephrosis

FIG C *Focal endocarditic glomerulonephritis* ("focal embolic glomerulonephritis") simulating the lesion of diabetic glomerulosclerosis

FIG D *Unusual variant of focal endocarditic glomerulitis* in a nondiabetic with subacute bacterial endocarditis, simulating the so-called diffuse diabetic glomerulosclerosis

The peripheral dilatation of capillaries about the amyloidotic spheres is similar to that about the lesions of diabetic glomerulosclerosis. In our material, the Foot modification of the Bielschowsky stain reveals little argyrophilia in *glomerular amyloidosis in contrast to the argyrophilia* of diabetic glomerulosclerosis and in contrast to the result published by King. Even in the latter case, the argyrophilia of amyloidosis lacked the constant laminations of the silver fibers of diabetic glomerulosclerosis.

*Nonspecific glomerulosclerosis of atrophic kidneys*

Sclerotic glomeruli of atrophic glomerulonephritis, pyelonephritic, nephrosclerotic (benign) and infarcted kidneys have been mistaken for the sclerosis of diabetic glomerulosclerosis (plate 245, 246). If the clean sharpness of outline of the nodular diabetic lesion, along with the peripheral capillary ring and nuclei, as well as the contrast with the thin-walled capillaries of the other parts of the tuft, is kept in mind, this type of error in diagnosis may be avoided.

*Chronic lobular glomerulonephritis*

Second to the lesions of glomerular amyloidosis, *chronic lobular glomerulonephritis is most* easily confused with diabetic glomerulosclerosis. The problem is made especially difficult because both lesions may be accompanied by the nephrotic syndrome. The lesions of lobular glomerulonephritis tend to be of uniform size and to involve every glomerulus in both kidneys (plate 80, 245E). In addition, the peripheral capillaries about the hyaline sphere are likely to be reduplicated and slightly frayed in contrast to the delicate wall of the peripheral capillaries about the diabetic hyaline spheres. The differentiation, therefore, may be made with routine stains. As an additional differential fact, however, it should be mentioned that with the silver stain the spherical lesions of chronic lobular glomerulonephritis are found to be made up of a mass of short curlycues of silver fibrils in contrast to the laminations of diabetic glomerulosclerosis (plate 243).

*Focal endocarditic glomerulonephritis*

Occasionally the collagenized lesion of focal endocarditic glomerulonephritis simulates diabetic glomerulosclerosis. Here, too, the endocarditic lesions lack the sharp outlines and peripheral capillaries of the diabetic spheres and, moreover, are prone to be irregularly fused with Bowman's capsule or adjacent capillaries. *The silver stain also reveals them to be made up* of irregular fibrils (plate 244).

*"Wire-loop" glomerulonephritis of disseminated lupus erythematosus*

In routine hematoxylin-eosin stains there need be no problem of differentiating the "wire-loop" lesions from those of diabetic glomerulosclerosis. The glomerular change of lupus erythematosus is an alteration of a portion of capillary wall that may swell into the capillary lumen as a verrucal hillock (plate 245B). However, the capillary change in this disease is a soft fibrinoid, brightly acidophilic swelling without an envelope of thin-walled capillaries. This fibrinoid alteration is not of the order of the dull hard dense hyalin of the diabetic glomerulosclerosis.

*Summary of Diabetic Glomerulosclerosis*

1. Diabetic glomerulosclerosis is a lesion spe*cific for diabetes mellitus if the rarest equivocal* cases are excepted.

2. Diabetic glomerulosclerosis occurs in one of three diabetic patients over the age of 40 and is extremely uncommon below the age of 30.

3. Patients with a few isolated lesions of diabetic glomerulosclerosis manifest no renal symptoms on this basis, those with widespread diabetic glomerulosclerosis very likely will have, in addition to the diabetes mellitus, hypertension, diabetic retinopathy, albuminuria, edema, hypoproteinemia, hypercholesterolemia and renal insufficiency. Prognosis is grave after the development of these signs and symptoms.

4. Sclerosis of the usually histologically neglected *efferent* arteriole is a common finding in association with diabetic glomerulosclerosis. As previously postulated, inasmuch as efferent arteriolosclerosis may be assumed to raise intraglomerular pressure, and inasmuch as angiotonin is stated to produce hypertension by constriction of the efferent arteriole, the possible role of organic narrowing of efferent arterioles in the hypertension of elderly diabetics is sug-

## PLATE 247. Renal Lesions in Diabetes Mellitus Other than Diabetic Glomerulosclerosis




Fig A *Diabetic glomerulosclerosis* in association with acute and chronic pyelonephritis. Diabetic glomerulosclerosis may be combined with a variety of renal lesions (A F I P Acc 71308)

Fig B *Glycogen vacuolization* of Armanni-Ebstein in the terminal portion of proximal convoluted tubules in a case of severe diabetes mellitus

convoluted

*tetrachloride*

## PLATE 248 Renal Lesions in Diabetes Mellitus Other than Diabetic Glomerulosclerosis




Fig A *Necrotizing papillitis and hydronephrosis* from a patient with diabetes mellitus and ureteral stenosis (Courtesy Dr W A D Anderson, *Pathology*, C V Mosby )

Fig B *Necrotizing papillitis* from a patient with diabetes mellitus There is a bland ischemic, infarct like necrosis of the papilla with a peripheral rim of leukocytes Similar lesions have been produced experimentally with chemicals such as vinylamine and thall

gested (Allen). Clearance studies in this connection might be of interest. Once again, however, the matter of limitations of the clearance studies must be raised. For example, it is noted that the *elevated* filtration fraction of 23 per cent, based on a study of one patient, has been interpreted as probably indicating increased constriction of the efferent arteriole (Rifkin et al ) Even if the resultant equivalence of constriction and the known organic narrowing of the efferent arterioles in diabetic glomerulosclerosis is allowed in deference to this interpretation, the effect of the multiple foci of "constriction" of the capillaries by diabetic glomerulosclerosis appears not to be included in the reckoning Such stenosis of glomerular capillaries may conceivably raise intraglomerular tension as effectively as constriction of efferent arterioles The hazards of the interpretation of the clearance studies is still further emphasized not only by the wide range of data but also by the disparity in the limited data inasmuch as other observers (Corcoran, Taylor and Page) noted a *diminished* rather than increased filtration fraction in patients with diabetic glomerulosclerosis Both groups of investigators agree that there is a reduction in glomerular filtration rate and renal plasma flow Twenty patients had urea clearances below 40 per cent (Rifkin).

5 Hyaline diabetic glomerulosclerosis shows no correlation with hyalinization of the pancreatic islets of Langerhans (Allen)

6 The marked dilatation of glomerular capillaries about the periphery of the lesions of diabetic glomerulosclerosis undoubtedly increases their permeability to proteins. It is suggested that this dilatation and permeability are responsible for the albuminuria which is one of the key disturbances of diabetic glomerulosclerosis (Allen) A similar histologic pattern occurs in glomerular amyloidosis and in lobular glomerulonephritis, in both of which conditions albuminuria is a pivotal disturbance

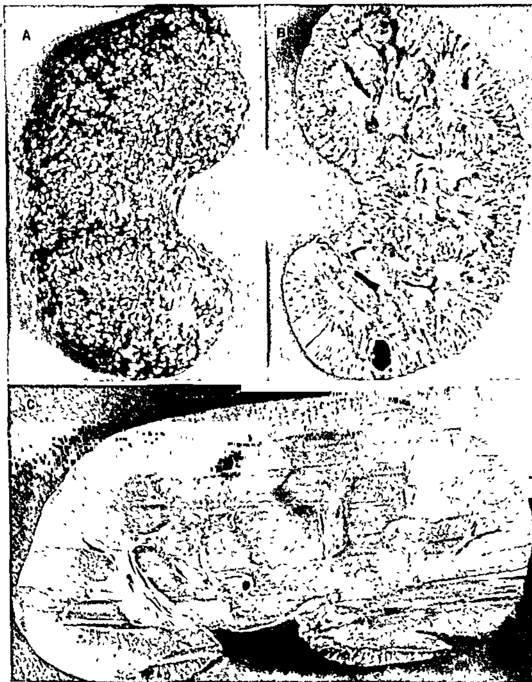
7. *Capillary* lesions corresponding to the glomerular lesions are *not* present in other parts of the body of diabetic patients, including even gangrenous legs. Lesions simulating those of diabetic glomerulosclerosis occur in the retina, but, again, there are definite histologic diffe ences.

8. Diabetic glomerulosclerosis *represen* sclerosis of the walls of the glomerular capi laries and not a sclerosis of the "mesangium between them (Allen). The lesions of diabet glomerulosclerosis are argyrophilic just as th basement membrane of normal capillaries i argyrophilic Sclerosis of supporting strom elsewhere does not result in a similar affinity fo silver. The precise localization of the lesion t the vessel wall in contrast to supportin stroma is of obvious pathogenetic importance especially in a disease such as diabetes mellitus in which generalized vascular sclerosis is the major unresolved problem

*Other Renal Lesions in Diabetes Mellitus*

Other renal lesions occurring in patients with diabetes mellitus include: (1) glycogenic vacuolization of the loops of Henle (Armanni-Ebstein vacuoles) (plate 247B), (2) osmotic nephrosis, (3) fat nephrosis (plate 247C), and (4) necrotizing papillitis (plate 248).

1. *Glycogenic vacuolization* occurs in the kidneys particularly of uncontrolled diabetic patients, and except for the rare von Gierke's disease, and possibly de Toni-Fanconi's syndrome, is specific for diabetes mellitus Whereas it was a common lesion in the preinsulin era (Warren), it has become an exceedingly infrequent finding It is characterized by empty-appearing cells, the eosinophilic cytoplasmic granules of which have been replaced by fluid which is colorless with hematoxylin-eosin but stains as red granules with Best's carmine. The loops of Henle are involved almost exclusively. The nuclei are moderately pyknotic. No renal disturbance has been proved to result from these glycogenic deposits. Their relation to changes in the phosphatase content of the tubular epithelium remains to be demonstrated. This is mentioned for the patent reason that the transport of glucose across the tubular as well as intestinal epithelium is presumed to be dependent on the enzymatic hydrolysis of hexosephosphate. The explanation of the deposition of glycogen in the loops of Henle offered by Oliver (1950) is that the cells of the proximal portions of the nephron are "used" to handling glucose




FIGS. A AND B. *Amyloidosis of kidney with secondary contraction.* When hypertension is present with renal amyloidosis, this type of contracted kidney is likely to be found.

FIG. C. *Amyloidosis of kidney* without contraction, representing the more usual picture. The kidney is enlarged and firm, the resistance to cutting is reflected in the uneven marks produced by the knife.

whereas the cells of the loops of Henle are "unaccustomed" to contact with high concentrations of glucose and so polymerize the glucose to glycogen.

2 *Osmotic nephrosis,* as previously described (page 207; plates 106-110) consists of a fine tracery of vacuoles in the cells of the proximal tubules. These vacuoles may be produced with the administration of infusions of glucose apparently as a result of excessive concentrations of glucose in the proximal tubules. This oncotic condition appears to be reproduced in diabetic patients who spill glucose into the urine Such vacuoles have frequently been mistaken for glycogen without the check of special stains Actually they are hydropic and quite like those produced by hypertonic sucrose

3 Fat nephrosis is described on page 218

4. *Necrotizing papillitis* is discussed on page 348

### Renal Amyloidosis

The understanding of the available facts about renal amyloidosis has been somewhat clouded for several reasons. First, there is the confusion arising from the existence of the terms "para-amyloidosis" or "atypical amyloidosis." These terms refer to the occurrence of hyalinized, usually weakly, if at all, metachromatic, collagenous tissue present as sclerotic foci, or as actual palpable masses, in locations that would be atypical for ordinary amyloid These locations include the skin, tongue, larynx, myocardium, articular and periarticular tissues, bone and cartilage; they rarely include the organs commonly involved in the banal form of amyloidosis, namely, the kidney, liver, spleen, adrenal glands and intestine. The etiology of para-amyloidosis is unknown; it is the form generally found with multiple myeloma

The *typical form* of amyloidosis is usually associated with chronic suppuration, as in tuberculosis, bronchiectasis, empyema, chronic abscesses and osteomyelitis, with a small percentage of various kinds of tumors, and with syphilis In isolated instances, no apparently pathogenetically related disease is present. Experimentally, typical amyloidosis may be caused by the production of chronic suppuration or by the injection of various proteins, such as living or dead bacteria, toxins and casein or its sodium salt (Kuczynski; Jaffé). Amyloidosis may be developed in rabbits in 11 days (Krawkow), the time required for the production of human amyloidosis is usually a matter of months or years although periods as short as three weeks have been reported Jaffé has increased the resistance to the occurrence of amyloidosis in mice with cholesterol feedings and, in some instances, with beef heart powder.

Second, confusion has arisen from the fact that the renal pathology has been pedagogically stuffed into the ill-fitting grab-bag of "nephrosis" and so the disease of the kidney has been called "amyloid nephrosis" with a consequent misdirection of attention to the renal tubules instead of the glomeruli. The result, once again, is that the attempt to explain the physiology of renal amyloidosis on this basis becomes awkward and forced since such an explanation is not predicated on the essential histologic change in the glomeruli

amyloidosis, indicates that the patient had the clinical nephrotic syndrome

Fig B *Glomerular amyloidosis* showing origin *within the capillary walls*

Fig C *Acute diffuse exudative glomerulonephritis* combined with glomerular amyloidosis

Fig D *Glomerular amyloidosis* illustrating partial amyloidotic conversion of the afferent arteriole Note that the amyloid is not merely on the inner side but involves the full thickness of the wall, a feature that applies also to the capillaries, since they are extensions of the afferent arteriole.

Fig E *Dense casts* in renal amyloidosis




(Legends on facing page)




FIG A *Diffuse glomerular amyloidosis*

FIG B *Amyloidosis of renal tubules and vessels*

FIG C *Amyloidosis of skin.* This material stains metachromatically Amyloid may be confined to the skin or may be part of a generalized amyloidosis. Cutaneous amyloidosis, however, is often part of para-amyloidosis or atypical amyloidosis

FIG D *Experimental amyloidosis of rabbit* The fatty vacuolization of the proximal tubules corresponds to the picture in some of the amyloidotic kidneys in humans

## PLATE 252. Generalized Arteriolo-Capillary Thrombonecrosis with Thrombopenia




Fig A *Massive cerebral hemorrhages* in a case of generalized arteriolar and capillary thrombonecrosis The cerebral hemorrhages are usually petechial in this disease

Fig B *Acute focal glomerulitis* in a case of generalized thrombonecrosis This lesion was present in very few of the glomeruli Scattered granules of hemosiderin are in the epithelium of the proximal tubules

### *Clinical Picture*

Renal amyloidosis may be entirely masked by the primary illness; it may result in mild urinary changes; or it may dominate the clinical picture. In any case of chronic suppuration, *tuberculosis or old syphilis, amyloidosis should* be considered If in such a case, there is also a clinical picture of the nephrotic syndrome (that is, anasarca, hypoproteinemia, hypercholesterolemia, reversal of albumin-globulin ratio, and albuminuria) it is extremely likely that renal amyloidosis is present. The retention of the intravenously injected solution of the colloidal dye, Congo red, is practically diagnostic of amyloidosis The Congo red test is usually normal in paramyloidosis. In amyloidosis, from 40 to 100 per cent of the dye leaves the blood stream within an hour to stain the amyloidotic tissue Exceptionally, Congo red may disappear from the blood stream with abnormal rapidity in the absence of amyloidosis (Bennhold). Hypoproteinemia itself appears to be a factor in the rapid removal of Congo red

*Oliguria* with high specific gravity of the urine usually occurs, as in other types of the nephrotic syndrome Polyuria, occasionally marked, may be the first indication of amyloid disease When associated with a low specific gravity, the polyuria is evidence of renal insufficiency, probably of the contracted variety of renal amyloidosis The proteinuria, which tends to be variable, may be as great as 30 Gm. daily, an amount approaching the severest forms of chronic glomerulonephritis with edema ("lipoid nephrosis") The loss of protein in the urine, as with other cases of protracted proteinuria, is probably the major factor in the accompanying hypoproteinemia, the reversal of the albumin-globulin ratio, and possibly also, by mechanisms as yet unknown, the hypercholesterolemia

Relatively more globulin appears to be lost in renal amyloidosis than in the nephrotic syndrome due to other lesions (Geill) In one case the blood cholesterol reached a level of 920 mg per cent (Linder et al.). Fishberg points out that the cachexia which may accompany amyloidosis may interfere with an anticipated elevation in the cholesterol level. Similarly, cachectic edema may occur and be mistaken for edema of renal origin. The involvement of the liver with amyloid may also lead to hypoproteinemia and edema, which may be mistakenly attributed to the kidneys

*Casts* in the urine are of the hyaline, granular, waxy and epithelial variety but they are relatively few in number Doubly refractile bodies, debris and cells, are commonly found in the urine just as they are in the urine in patients with the nephrotic syndrome of diabetic glomerulosclerosis or chronic glomerulonephritis Pyuria and hematuria are not present as a rule.

*Azotemia* as a result of renal amyloidosis occurs infrequently, and may be absent even with extensive glomerular amyloidosis Only 40 cases of renal amyloidosis and associated hypertension have been recorded in the literature (Leard and Jaques), most of these were instances of contracted amyloidotic kidneys

*Disappearance of amyloidosis* has been reported in mice (Kuczynski) and, in rare instances, in man (Reimann).

### *Pathology*

#### *Gross appearance*

Typically the kidneys with extensive amyloidosis are diffusely enlarged to about one and one half times normal size; in extreme cases each kidney may weigh over 400 Gm. The capsule is easily stripped over a smooth yellow-brown surface In the process of cutting the kid-

FIG A *Generalized arteriolo-capillary thrombonecrosis* involving the kidneys

FIG B *Interlobular arteritis* with thrombosis, marked endothelial hyperplasia, and luminal dilatation The associated glomerulus is not remarkable

FIGS C AND D *Interlobular arteritis and thrombosis* with focal fibrinoid degeneration from a case of fulminant thrombopenia, purpura and death in several weeks The markedly dilated vessel resembles a tubule The glomerulus shows slight increase in cellularity. Hemosiderin granules,

PLATE 253. Generalized Arteriolo-Capillary Thrombonecrosis with Thrombopenia




(Legends on facing page)

## PLATE 254.—GENERALIZED ARTERIOLO-CAPILLARY THROMBONECROSIS WITH THROMBOPENIA

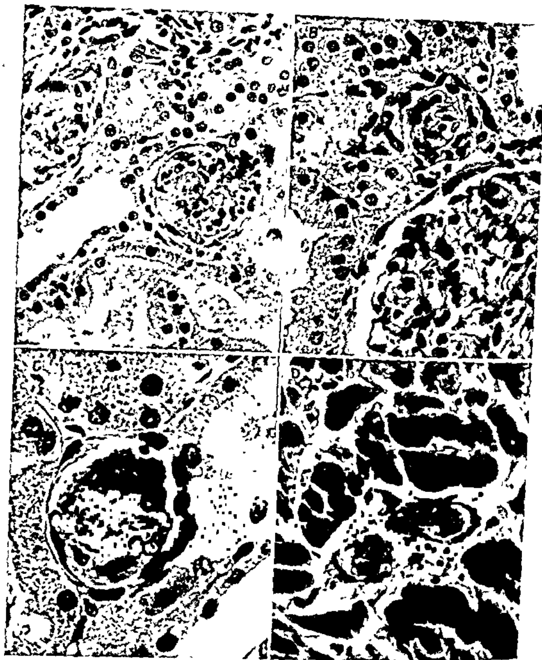



FIG A *Smudgy homogenous fibrinoid necrosis* of portions of the afferent arteriole is evident

FIG B *Distinct thickening* with focal, obviously intramural fibrinoid degeneration is noted in this afferent arteriole

FIG C *Fibrinoid necrosis* with hyperchromatism of cells of the arteriole is noted in this partially thrombosed vessel

FIG D *Arteriolocapillary thrombonecrosis* of the myocardium The necrosis of vessel walls appears to be the starting point of the platelet-like verruca originating and developing directly in the wall

ney, the knife meets a characteristic tough resistance that, by itself, suggests the diagnosis (plate 249) On inspection the sectioned surface resembles that of the large "white" kidney of chronic membranous or lobular glomerulonephritis ("lipoid nephrosis") because of the yellow-brown or ochre color, the widened cortex, and the tough waxy consistency The tan cortex and brown medulla are fairly sharply demarcated The glomeruli are visible by oblique light as enlarged, greyish, translucent appearing dots The vessels are not remarkable grossly The application of Lugol's solution after dilute acetic acid reveals a dark brown stain at the sites of amyloid deposition

Infrequently the kidneys with amyloidosis have granular rather than smooth surfaces (plate 249A, B) These represent the "contracted" kidneys which, despite the scarring, rarely weigh or measure less than normal presumably because of the compensatory increase of the fatty tubules and edematous interstitium An analagous situation obtains in the case of diabetic glomerulosclerosis

*Histologic appearance*

*Glomeruli* The *glomeruli* are the site of principal change when the fullblown picture of the nephrotic syndrome is present The glomerular tuft is converted into multiple, homogeneously pink (hematoxylin-eosin) spheres, closely simulating the lesions of diabetic glomerulosclerosis (plate 250). The spheres take the metachromatic stains for amyloid (e g , Congo red, crystal violet) The amyloidotic material represents a nodular conversion of the walls of the glomerular capillaries rather than a deposit of a substance on their luminal aspect or in the intercapillary tissue This feature of the lesion can be traced not only in serial sections but also in a single section in which the initial stages of amyloidotic thickening of the capillary walls are evident (plate 250) In other words, the amyloidosis represents an in situ conversion of pre-existing reticulin or collagen, rather than an accretion of material deposited on the inner aspect of a basement membrane The distinction clearly is of pathogenetic importance

There is some tendency for the peripheral capillaries to be dilated about the hyaline spheres but this feature, as well as the layering of nuclei at the rim of the spheres is not nearly as marked as in diabetic glomerulosclerosis. Moreover, the spheres are usually not quite as sharply circumscribed as the diabetic lesion In further contrast, the amyloid spheres of the glomeruli are often marked by artefactual linear streaks reflecting the different densities of the two lesions (plate 245A) When a single glomerular sphere is present in diabetic glomerulosclerosis, it is likely to be situated opposite the vascular pole, there is no such tendency in glomerular amyloidosis The differential pattern with the silver stain is striking (plate 243, 244) Finally, the efferent arteriole is commonly thickened in association with diabetic glomerulosclerosis but is infrequently involved with amyloidosis (plate 241E, F)

The very early stages of glomerular amyloidosis may be mistaken in routine stain (hematoxylin-eosin) for the capillary sclerosis of benign nephrosclerosis However, in the early glomerular amyloidosis, the thickened capillary walls have a soft, almost smudgy, rather than dense, appearance of benign nephrosclerosis

*Vessels* The amyloidosis tends to involve the smaller renal vessels, especially the afferent arterioles, interlobular arteries, and arcuate arteries The afferent arterioles may be markedly dilated and thickened at the hilum (plate 250D) The media particularly, but also the intima and even the adventitia of the larger vessels may be involved Amyloidosis may also involve the interstitial collagen abundantly

*Tubules* The tubules in a given kidney may show one or all of the following changes:

1 Fatty vacuolization of the epithelium of the proximal tubules (plate 251D) Much of the fat is anisotropic as in the tubules of diabetic glomerulosclerosis, and chronic lobular or membranous glomerulonephritis This tubular change occurs when there is extensive glomerular amyloidosis along with the clinical nephrotic complex
2 Amyloid thickening of the tubular basement membrane (plate 251B) which may reach an extreme degree
3 Dense hyaline casts in the distal convoluted tubules (plate 250E) and below It is prob-

PLATE 255. Shock: Intraglomerular Capillary Thrombosis




Fig A *Intraglomerular capillary thrombosis with small early infarction* in shock The necrosis of the epithelium of the more vulnerable proximal tubules is evident in contrast to the better preserved epithelium of the pale staining distal tubules Droplets of fat in the tubular epithelium may occur in shock

Fig B *Intraglomerular capillary thrombosis in shock* and dehydration




FIG. A *High magnification of capillary thrombosis in shock* with dehydration the thrombotic material resembles fibrin but it is, in reality, packed, partially laked, red blood cells

FIG. B *Glomerular capillary thrombosis* occurring in shock associated with dehydration

FIG. C *Renal infarct* in shock without associated vascular thrombosis The necrosis is the result of ischemia from local diversion of the flow of blood

able that these dense obstructive casts are in considerable measure responsible for a large *proportion of the tubular atrophy.*

4. *Much of the tubular atrophy* appears analagous to the atrophy secondary to the dense casts in the kidney in multiple myeloma. Glomerular amyloidosis and narrowing of *arteries and arterioles by the amyloidosis* also must contribute in some part to the tubular atrophy. As far as the glomerular contribution is concerned, it is curious that in some cases with extreme glomerular in*volvement, the tubules may show no sig*nificant atrophy. This disparity between the degree of the glomerular and tubular involvement may occur also in acute glomerulonephritis.
5. Conspicuous hyaline granules, or hyaline droplets are seen in the epithelium of the convoluted tubules. For reasons discussed in the section under "Hyaline Granule Nephrosis," these are regarded as an intrinsic cytoplasmic alteration rather than as granules of protein reabsorbed from the tubular lumen.

The kidneys are rarely the only organs involved by amyloidosis, on the other hand, the liver and spleen are frequently the sites of amyloidosis to the exclusion of the kidney.

## Generalized Arteriolo-Capillary Thrombonecrosis

### *Introduction*

In recent years there has been renewed interest in the disease first described by Moschkowitz in 1925, by 1948, 71 cases had been reported. The lesion is uncommon but not as rare as this small number of reports indicates. The diagnosis is almost never made clinically and has often been missed on histologic examination. The disease *is characterized by a sudden* onset of purpura, fever, thrombocytopenia, anemia and of an urticarial or other rash in about 25 per cent of cases. Hepatomegaly and splenomegaly occur occasionally. Headache, convulsions, delirium, coma, focal paresis and hemiplegias may accompany the picture. The course of the disease leads to death in from one to seven weeks. No age group is selectively involved, the reported range being from 9 to 66 years (Adams et al.). Clinically, the entire group of purpuras, and especially Werlhof's purpura, enters into the problem of differential diagnosis. The lack of a favorable response to transfusions separates this disease from Lederer's anemia with which it is was initially linked.

### *Pathology*

#### *Gross appearance*

Grossly, the essential changes are the effects of purpura. The prominent neurologic manifestations are also the result of the hemorrhagic diathesis although in only one case were massive cerebral hemorrhages demonstrated (plate 252A).

#### *Histologic appearance*

The essential histologic change involves the small *arteries, arterioles, and capillaries* in every organ of the body. Veins are not involved although some of the arterioles may be so dilated as to resemble veins. The organs with the fewest vessels involved are the lungs, a feature common also to other diffuse vascular diseases. The lumen of the vessels is occupied by a granular, eosinophilic material which projects eccentrically into the lumen from one *segment of* the wall (plate 253, 254). These "thrombi" do not entirely occlude the lumen but usually leave an irregular crescent of free space between their periphery and the intima. As a *rule, the periphery of the thrombi is lined by freshly proliferated endothelial cells* which may

---

FIG. A. *Massive ischemic infarction* of kidney due to *embolus in renal artery from a mural thrombus* in the heart.

FIG. B. *Renal ischemic infarct* due to embolus to arcuate artery. The zone immediately subcapsular is spared the necrosis, apparently because of col*lateral capsular circulation.*

FIG. C. *Remarkable case of unilateral cortical necrosis* in which thrombosis was present only in the sclerotic renal artery of otherwise negative *contralateral* kidney. Other photographs from this case are in plates 225 and 226.

PLATE 257. Ischemic (Arterial) Infarct

A

B



C



(Legends on facing page)

PLATE 258. ISCHEMIC (ARTERIAL) INFARCT




FIG A *Acute renal infarct* due to embolus to artery The epithelium of the distal convoluted tubules is better preserved than the epithelium of the proximal tubules which, as shown here, are completely necrotic

FIG B *Recent infarct* due to embolus to renal artery Much leukocytic reaction and hemorrhage are present.

FIG. C *Acute renal infarct* in periarteritis nodosa The leukocytic infiltrate is a reaction to the infarction and not of periarteritis nodosa.




FIG. A. *Mycotic (embolic) renal arteritis* with thrombosis and aneurysmal dilatation in a case of bacterial endocarditis. No infarct was present.

FIG. B. *Mycotic arcuate arteritis* [illegible] terial endocarditis. If such a lesion [illegible] would resemble the end result of [illegible]

FIG. C. *Medullary infarct* in a nondiabetic, simulating necrotizing papillitis. [illegible] cases of necrotizing papillitis are filed away as simple medullary infarcts.

also canalize a portion of the "thrombi" The endothelial cells or fibroblasts may be so numerous as to form a cellular mass and obscure the lesion (plate 253D)

The vessels themselves, especially the afferent arterioles, may be so dilated as to be mistaken for venules or even tubules (plate 253B, C). Serial sections of these vessels invariably reveal a focus of fibrinoid swelling in a segment of their walls and it is usually at this site that the "thrombus" is initiated (plate 254) This same type of fibrinoid damage may be seen in its early stages as a mural hillock of fibrinoid degeneration *without attached "thrombi,"* as demonstrated in serial sections (plate 254). This is the essential quality and pattern of change observed in other sites in this condition, and in other diseases, as in the typhus fevers (Allen and Spitz), and in the valvular changes of endocardiosis, rheumatic valvulitis, bacterial endocarditis and Libman-Sacks endocarditis (Allen and Sirota) In these latter instances, intrinsic fibrinoid changes directly in the collagen of vessels and valves with internal exudation of *plasma into their walls simulate external accretion* of thrombi from the lumen In the case of the generalized vascular "thrombosis," the material in the lumen can not be unequivocally distinguished from platelet thrombi by current histologic methods although some observers (Engel et al) call attention to tinctorial discrepancies between these "thrombi" and unquestionable platelet thrombi The impression gained by us is that these "thrombi" actually represent clotted and partially organized plasma which has been exuded into the lumen from that portion of the vascular wall which has undergone fibrinoid swelling. In other words, the disease appears to be primarily a diffuse vascular disease in much the same sense that periarteritis nodosa is. In this connection, it is of interest that many patients with this acute disease, that is, generalized arteriolo-capillary thrombonecrosis, have a history of allergy with urticaria The thrombocytopenia might better be related, however nebulously at present, to some such factor as allergy or toxicity, rather than to the withdrawing of platelets from the peripheral blood to form the "thrombi," a mechanistic theory suggested originally by Klemperer, Baehr and Schifrin. After all, if all of these thrombi were packed together, there is no arithmetical reason to believe that they would outnumber the platelets that go into the formation of some huge blood clots unassociated with thrombopenia On the other hand, the association of allergy and thrombopenia is a long recognized phenomenon.

The bone marrow shows no specific qualitative change in its cellular elements, including the megakaryocytes, the latter may be somewhat increased. However, the vascular lesions occur also in the marrow and a biopsy could be the source of an antemortem diagnosis (Fitzgerald et al.)

## Shock

Several varieties of renal lesions have either a direct or intermediate pathogenetic relationship to shock. These are·

- Diffuse glomerular thrombosis.
- Intrarenal venous thrombosis
- Fatty degeneration or necrosis of proximal tubular epithelium.
- *Hemoglobinuric ("lower nephron") nephrosis.*
- Renal infarction.
  - Isolated.
  - Bilateral cortical necrosis.

### *Diffuse Glomerular Thrombosis*

There occurs in shock, particularly when associated with severe dehydration, a form of diffuse thrombosis of the glomerular capillaries. The thromboses may involve a few peritubular capillaries, but they are practically confined to the glomeruli (plate 255, 256) Organs other than the kidney are not affected Thrombi are occasionally fibrinous, but more often they merely simulate fibrin and are in reality freshly clumped masses of erythrocytes which have provoked no other glomerular histologic reaction (plate 256A). The lesions are obviously preagonal and are not responsible for renal insufficiency of more than several hours' duration, if at all These thromboses have been observed not only in nonspecifically shocked, dehydrated patients, but also in carbon monoxide poisoning and in plague (Ash and Spitz) (plate 159B) The lesion is not to be confused with the

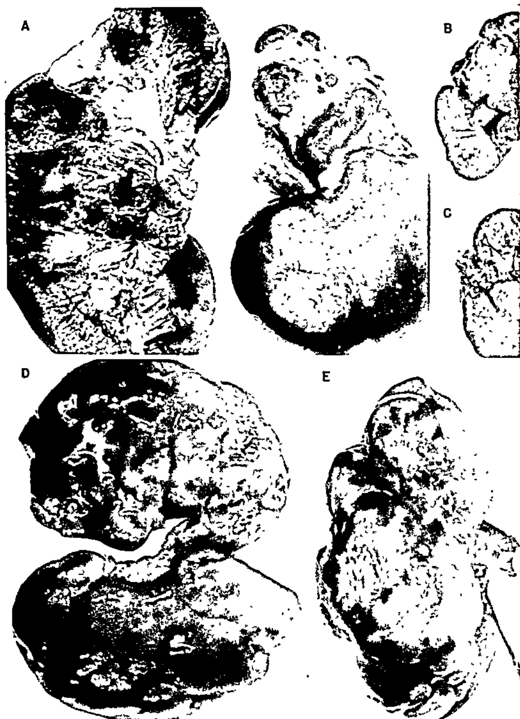



FIG. A. *Old infarcts of kidney* due to emboli of renal artery. The depth and irregularity of the scars of infarction are illustrated.

FIGS. B AND C. *Organized infarcts* of kidney due to embolism from cardiac mural thrombi. The depth of the depression is to be contrasted with the shallow scars of pyelonephritis.

FIGS. D AND E. *Old and recent infarcts* of varying ages.

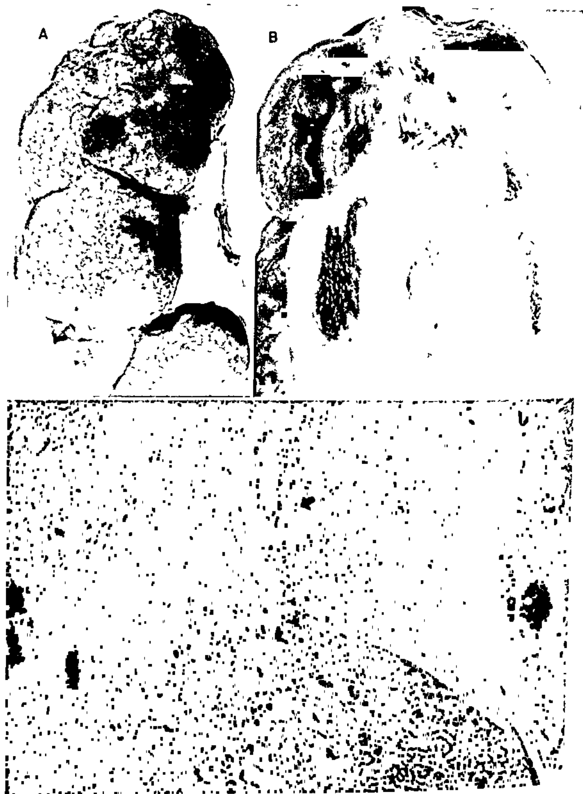



FIG A *Distortion of renal surface* due to old arterial infarcts

FIG B. *Recent and old arterial infarcts* due to embolism from cardiac mural thrombi.

FIG C *Healed renal infarct* demonstrating cortical depression, the hyalinized glomeruli (arrow), and the overlying, thickened, adherent vascularized capsule




Fig. A *Old infarct* showing cortical depression at site of scarred atrophic parenchyma

Fig. B *Fibrotic glomeruli*, partially or completely scarred at the periphery of an infarct

Fig. C *Compressed cluster of atrophic hyalinized glomeruli* in the scar of an old infarct

occurrence of thrombosis in isolated capillaries in acute diffuse glomerulonephritis, in eclampsia, in malignant nephrosclerosis, in diffuse arteriolocapillary thrombonecrosis with thrombocytopenia, or with the verrucal capillary thickenings of the glomeruli in disseminated lupus erythematosus. One of the puzzling features of this lesion of glomerular thrombosis is its relatively infrequent occurrence

Of the remainder of the renal lesions in which shock is presumed to participate, hemoglobinuric ("lower nephron") nephrosis, and bilateral cortical necrosis are of chief concern. These are discussed in detail separately. Focal fatty degeneration of the proximal tubular epithelium is common but is not clinically important Intrarenal venous thrombosis in shock is neither common nor of apparent importance (plate 263); necrosis of proximal tubular epithelium is also an infrequent manifestation of shock but it may be functionally significant when it does occur Isolated renal infarction as a result of shock is another unusual effect in humans (plate 256C)

## Renal Infarcts

Renal infarcts are produced by one of three basic hemodynamic mechanisms:

- Arterial
  - Embolism
  - Thrombosis
  - Organic narrowing
  - Functional—shock
- Venous (thrombosis)

Infarcts are of three kinds: (1) ischemic, (2) hemorrhagic, and (3) combined Arterial and functional infarcts are ischemic, venous infarcts are always hemorrhagic Occasionally there appear to be combined infarcts with both ischemic and hemorrhagic necrosis These usually are primarily ischemic infarcts with superimposed hemorrhagic admixture because of diapedesis, necrosis of walls of vessels, and secondary venous stasis and thrombosis in the smaller vessels This hemorrhagic reaction secondary to ischemic infarction is observed also in other organs, as, for example, in a myocardial infarct In some instances, however, combined infarcts are caused by simultaneous thrombosis of artery and vein

### *Clinical Picture of Renal Infarcts*

The signs and symptoms of renal infarcts are local pain, tenderness in the flank, shock, hematuria, and albuminuria The pain lasts from one week to ten days. A sudden rise of blood pressure, sustained over weeks, may occur as a result of the infarction In venous infarction, the kidney may become so engorged as to be palpable The retrograde pyelogram may or may not show some alteration Function of the affected kidney is likely to be diminished or totally absent, depending on the size of the involved area. The clinical diagnosis of renal infarction is generally overlooked The signs and symptoms of renal infarction may be mistaken for splenic infarction, renal neoplasm, paranephric abscess, essential hematuria, renal calculus, or a ruptured viscus

### *Pathology of Renal Infarcts*

The acute ischemic infarct is characteristically wedge-shaped, with the base of the triangle at the capsule, yellow to yellowish grey, and usually with a hemorrhagic border (plates 257, 260, 261). Several isolated infarcts may occur in the same kidney or the individual infarcts may coalesce to the extent of being indistinguishable from cortical necrosis of the kidney This similarity leads to noting that very often the necrosis is confined to the cortex and spares the medulla, as it generally does in bilateral cortical necrosis (plate 230A)

In the *healed state*, the infarcted area appears as a deeply depressed area with the capsule usually increased in thickness, highly vascularized, and strongly adherent to the cortex in the area of infarction (plate 261). The altered appertaining artery leading to the area may be identified in many instances The scar of the infarct may become irregularly calcified Occasionally, the residuum of an old infarct is cystic, secondary to liquefaction degeneration of the infarcted tissue in the early stage

The *hemorrhagic infarct* almost always takes the form of hemorrhagic necrosis of the entire kidney, such as occurs particularly in the newborn, after thrombosis of the renal vein

Histologically, there is little to record about the nature of the infarcts that is not more adequately illustrated in the photomicrographs

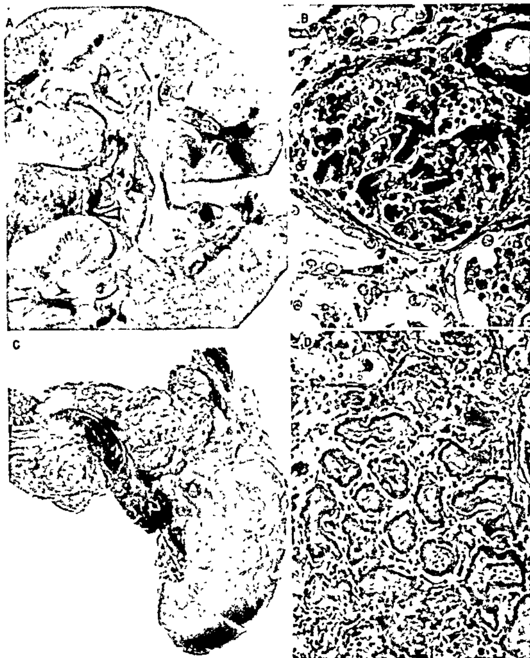



FIG. A. *Acute thrombosis of several days' duration of renal veins* and their small tributaries. No renal infarcts were present. The kidneys were not insufficient.

FIG. C. *Thrombosis of renal vein* following splenorenal venous anastomosis for cirrhosis. The renal parenchyma showed no noteworthy changes.

FIG. B. *Thrombosis of glomerular capillaries* following thrombosis of renal veins (from kidney of figure A).

FIG. D. *Small infarct* following thrombosis of small tributary of renal vein in an adult.

occurrence of thrombosis in isolated capillaries in acute diffuse glomerulonephritis, in eclampsia, in malignant nephrosclerosis, in diffuse arteriolocapillary thrombonecrosis with thrombocytopenia, or with the verrucal capillary thickenings of the glomeruli in disseminated lupus erythematosus. One of the puzzling features of this lesion of glomerular thrombosis is its relatively infrequent occurrence

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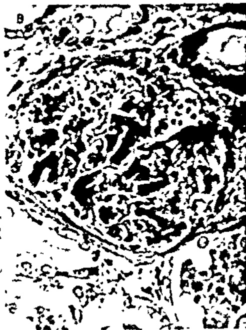









Fig. A. [illegible]

Fig. C. [illegible]

Fig. B. [illegible]

Fig. D. [illegible]

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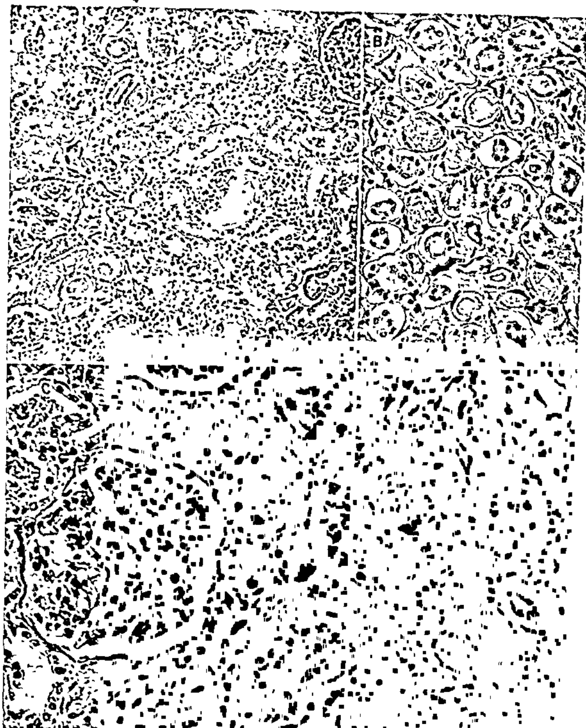
Fig. A. [illegible] of renal [illegible] The kidneys were [illegible]

Fig. C. Thrombosis [illegible] The renal [illegible]

Fig. B. Thrombosis [illegible] of renal [illegible] Figure A.

Fig. D. [illegible]

## PLATE 264. Chronic Thrombosis of Renal Veins




These photomicrographs show the relatively mild changes in renal parenchyma following long standing thrombosis of main renal veins with an associated clinical syndrome simulating lipoid nephrosis Scattered slight interstitial fibrosis, tubular degeneration and protein casts are noted

PLATE 265 CHRONIC THROMBOSIS OF RENAL VEINS



(plates 258, 261C, 262) The ischemic infarcts in the early stages are often rimmed by leukocytic as well as hemorrhagic borders (plate 258B, C). Evidence of regeneration, particularly of the proximal tubular epithelium, may be seen very early. The distal convoluted tubules may be viable in the midst of more vulnerable necrotic proximal tubules (plate 258A). Septic infarcts may contain purulent exudate throughout the area of necrosis. The healed stages are identified by the masses of closely packed hyalinized fibrotic residues of glomeruli and scar tissue in an indented wedged area with adherent capsular and pericapsular vascular scar (plates 261C, 262C) Necrotizing papillitis is occasionally regarded as a medullary infarct (plate 259C).

*Etiology of Arterial Infarcts*

Most of the arterial infarcts are caused by *embolism from cardiac mural thrombi complicating* myocardial infarctions, and from vegetations of subacute bacterial endocarditis *Infrequently*, emboli from verrucal endocardiosis, and atheromatous plaques or mural thrombi of the aorta may reach the kidney. Infarcts due to thrombosis of the renal artery are the result principally of periarteritis nodosa and mycotic arteritis Thrombosis of the renal artery occurs also secondary to sclerotic narrowing and rarely from thromboangiitis obliterans and syphilitic endarteritis Arterial infarcts may follow marked narrowing of renal arteries or their branches as a result of sclerosis or periarteritis nodosa, for example, without actual thrombotic occlusion The mechanism in these instances is renal arterial insufficiency and the infarcts are not necessarily ever acute but rather may be of the torpidly progressive ischemic type that is commonly seen in the kidneys with marked arteriosclerosis In addition, acute infarcts on a functional basis may occur in shock (Penner and Bernheim), or as a result of the action of certain poisons or drugs. The ultimate example of infarction on a functional basis is bilateral cortical necrosis (plate 266). A remarkable example of functional infarction is illustrated in plates 225 and 226 In this case, which was *cited previously* in regard to the pathogenesis of hypertension (page 412), thrombosis of a sclerotic left renal artery occurred in a hypertensive white male, 52 years of age; despite the thrombosis, the parenchyma of this kidney was not altered, but cortical necrosis occurred in the opposite right kidney. The right kidney showed prominent arteriolosclerosis and intrarenal arteriosclerosis in sharp distinction from the left kidney in which only the extraparenchymal renal arteries were sclerotic, thus behaving in effect as a Goldblatt clamp.

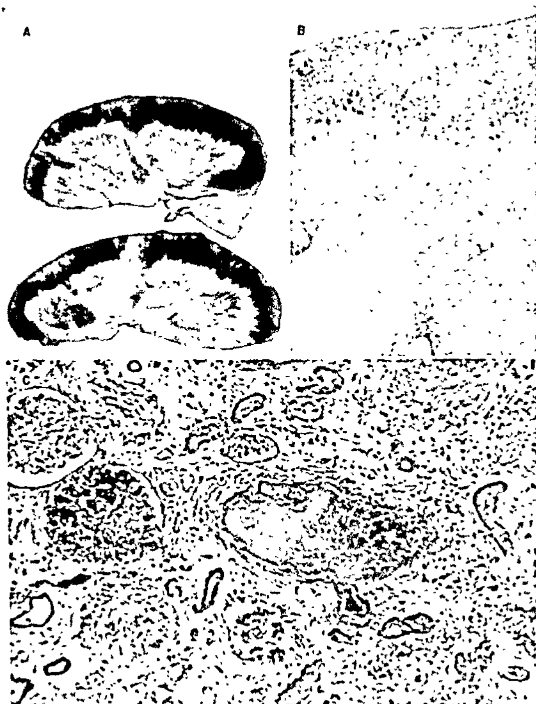
Occasionally, the main renal artery appears completely occluded by thrombosis without apparent destruction of the parenchyma, as in the case just cited, or with only mild atrophy of the kidney as illustrated in plate 227. The explanation must reside in the presence of adequate but not always evident collateral circulation

*Thrombosis of Renal Veins*

*The effect of thrombosis of the main renal* vein is generally although not always different in adults and infants.

*In infants, particularly newborn infants,* thrombosis of the main renal arteries is associated with a massive hemorrhagic infarction of the kidneys This type of infarction has been observed in infants, especially those with severe diarrheal diseases and marked dehydration Although previously considered to be rare, total hemorrhagic renal infarctions were observed in 4 of 25 autopsied cases of infants with severe epidemic diarrhea (Barenburg et al ). In two of these, the infarction was accompanied by thrombosis of the main renal vein; in the other two, the veins were not involved. When present, the thrombus is generally confined *to the main* renal vein In the case of Marshall and Whapham, bilateral massive hemorrhagic infarction was noted in a newborn infant *in the absence of* thrombosis of the main renal veins. In this case there was no diarrhea or apparent infection. In *6 of 8 clearly documented cases* of hemorrhagic infarction of the kidney collected from the literature by Regan and Crabtree, the patients *were infants* and thrombosis of the main renal veins occurred in each The associated diseases were gastroenteritis in 4, lobular pneumonia in 1, and cellulitis extending from an abscess of the groin in 1. The ages of these 6 patients (5 males,

PLATE 2[illegible]. ARTERIAL AND ARTERIOLAR INSUFFICIENCY. BILATERAL CORTICAL NECROSIS



(plates 258, 261C, 262). The ischemic infarcts in the early stages are often rimmed by leukocytic as well as hemorrhagic borders (plate 258B, C) *Evidence of regeneration, particularly* of the proximal tubular epithelium, may be seen very early. The distal convoluted tubules may be viable in the midst of more vulnerable necrotic proximal tubules (plate 258A). Septic infarcts may contain purulent exudate throughout the area of necrosis. The healed stages are identified by the masses of closely packed hyalinized fibrotic residues of glomeruli and scar tissue in an indented wedged area with adherent capsular and pericapsular vascular scar (plates 261C, 262C). Necrotizing papillitis is occasionally regarded as a medullary infarct (plate 259C)

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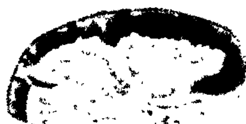
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1 female) were 9 days (Heller), 13 and 29 days (Campbell and Matthews), 2 months (Aschner), 3 months (Gruneberg), and 2 years (Fuhr). Three of these infants survived nephrectomy. The two other cases were in adults aged 20 years (Danhiez) and 33 years (Melick and Vitt), who developed the infarction apparently 5 days and 65 days postpartum respectively In one case, recently reported, the mother of a 7 day old infant had had a toxemia of pregnancy (Cabot case 36032) In this case there was anuria from the time of birth and azotemia up to a level of 220 mg per cent (NPN). Hemorrhagic infarction occurred in only one of the kidneys—the one with the thrombosis of the main renal vein—but intrarenal venous thromboses were present in both kidneys Bilateral total hemorrhagic infarctions of the kidneys are, of course, invariably fatal The patient with unilateral massive hemorrhagic infarction may occasionally be saved by prompt nephrectomy.

The cases of hemorrhagic infarction occurring without thrombosis of the renal veins raise the possibility that when such thrombosis is present, it is secondary to the infarction, or, at least, not the cause of it While it does appear to be a fact that hemorrhagic renal infarction may take place without significant thrombosis of renal veins, it is nevertheless true that in most cases, the venous thrombosis caused the infarction. No other interpretation is plausible in those instances in which renal infarction occurred after the thrombosis extended into the renal veins from the inferior vena cava. What remains unclear is (1) the reason for the relatively high incidence of these hemorrhagic infarctions in infancy and particularly in the neonatal period, (2) the reason for the total infarction without an organic vascular basis in some of the cases, and (3) the reason for the thrombosis of the renal vein in the presence usually of gastroenteritis Bacteriologic and histologic studies of the thrombus and the wall of the vein in these instances are not illuminating

*Renal Vein Thrombosis in Adults*

In the adult, thrombosis of the main renal vein produces, generally, not hemorrhagic infarction (plate 263C), but a clinical picture of the nephrotic syndrome (Derow et al; Bell) (plate 264); hypertension was also present in Bell's case which followed nonlethal exposure to hydrogen cyanide. The nephrotic syndrome appears to be principally on the basis of the protracted loss of protein, especially albumin, in the urine as a consequence of abnormal glomerular permeability from the transmitted effects of increased venous pressure In line with this is the suggestion that orthostatic albuminuria may be caused by pressure on the left renal vein as an effect of lordosis Recently, it has been shown experimentally that increased pressure in the main renal vein results in an increased reabsorption of salt and water (Blake et al); these factors ould, of course, enhance the edema of the nephrotic syndrome secondary to thrombosis of the renal veins

With severe proteinuria, there ensues hypoproteinemia, reversal of albumin-globulin ratio, hypercholesterolemia, edema—a mechanism and sequence of events that is a common denominator of other forms of the clinical nephrotic syndrome. Kidneys in patients with the nephrotic syndrome secondary to thrombosis of the main renal vein exhibit little alteration in contrast to those of the newborn The nephrotic kidneys are slightly to moderately enlarged and histologically show little more than moderate tubular atrophy and interstitial edema with fibrosis (plate 264) Again, the reason for this tremendous disparity in reaction to venous thrombosis in infants and adults must be the *difference in collateral circulation* available. In plate 263, for example, diffuse intrarenal thrombosis secondary to shock is illustrated in the kidney of an adult in which minimal histologic changes were present.

### Cortical Necrosis

Bilateral cortical necrosis (symmetrical cortical necrosis) was first described by Juhel-Rénoy in 1886; the patient was a 16 year old girl with scarlet fever. Up to 1941, 71 cases had been reported (Duff and More) In recent years, interest in this dramatic clinical and pathologic entity has been revived, particularly *on the* basis of the experiments of Trueta and his colleagues on renal hemodynamics

### *Etiology*

Bilateral cortical necrosis occurs predominantly but not exclusively during pregnancy. It may follow poisoning by diethylene glycol, dioxane, dipropylene glycol, methyl and butyl carbitol, the administration of camphor intravenously, thyroid extract, cobra venom, and alcohol, and it may occur in association with burns, shock and with various infections such as diphtheria, scarlet fever, cholera, pneumonia, dysentery and therapeutic malaria Unilateral cortical necrosis has followed thrombosis of the contralateral renal artery (plates 225, 226) Bilateral cortical necrosis is a different pathologic entity from the hemorrhagic infarction of the kidneys in infants with thrombosis of renal vessels

### *Clinical Picture*

The clinical signs and symptoms are essentially the same in all cases regardless of the underlying background Extreme oliguria or anuria, pain in the epigastrium radiating to the loins or along the course of the ureters, dependent or generalized edema in over a third of the cases and the terminal features of uremia comprise the clinical picture The blood pressure *shows no trend toward hypertension* Albumin, white blood cells, hyaline and granular casts are usually present in the urine The urine prior to the onset of anuria is generally grossly bloody Death occurs in from 2 to 32 days after the suppression of the urine In some patients, anuria is followed by oliguria before death.

Inasmuch as most of the cases, approximately two-thirds, are associated with pregnancy, this feature merits some elaboration. Less than two-thirds of the patients are multipara In about 85 per cent, the renal lesions occur prior to full term; in the remainder, the complication takes place near the time of delivery In one instance the anuria occurred 13 days after delivery (Iungano) In about 25 per cent, the pregnancy is otherwise uneventful, in the remainder of cases, preeclampsia or eclampsia is present, and the membranous glomerular lesions of this toxemia may be found in conjunction with cortical necrosis (plate 103). In almost 40 per cent of cases, there is some evidence of renal dysfunction antedating the cortical necrosis. Retroplacental hemorrhage is a frequently associated condition.

### *Pathology*

#### *Gross appearance*

The kidneys are moderately swollen and soft and the capsules are easily stripped from purple-red or red and yellow, mottled surfaces. Longitudinal sections reveal usually a spared, immediately subcapsular reddish brown strip of 1 to 2 mm., beneath which the remainder of the cortex is abruptly demarcated by a yellowish grey necrotic zone extending the length of the kidneys (plate 266A), including the cortical columns of Bertin. In some instances, the cortical involvement is incomplete and the cortical zone is made up of multiple grey infarcted wedges rimmed by deeply hyperemic margins. Usually the inner, or juxtamedullary half or third of the cortex is spared, but occasionally the entire cortex and rarely even the medulla (Scriver and Oertel) may be involved The renal vessels are not grossly altered although in one of our cases, a thrombosis of the contralateral, markedly sclerotic main renal artery was found (plates 225, 226)

In addition to necrosis of the kidneys, infarct-like necrosis of the anterior lobe of the pituitary (Doniach and Walker; Sheldon and Hertig) and of the tuber cinereum may be present Infarction of the anterior lobe of the pituitary gland attributed to shock, was noted also in one of our cases following an incompatible transfusion with resultant hemoglobinuric nephrosis (plate 129C).

#### *Histologic appearance*

As stated, the narrow subcapsular cortical zone is usually although not invariably intact, presumably because of collateral capsular circulation (plate 266A, B) This zone is bordered by hyperemic glomeruli and vessels as are the lower and lateral boundaries of the infarcted areas The necrosis of the cortical components, that is, glomeruli, tubules, interstitium and vessels, is essentially similar to that of single renal infarcts The extreme dilatation of glomerular capillaries (plate 266C) is a conspicuous feature which has been variously interpreted as reflecting vasoparalysis or a stage of

## PLATE 268. Renal Cortical "Shunt" of Trueta: Radiomicrographs of Kidney of Rabbit Following in Vivo Injection of Colloidal Bismuth

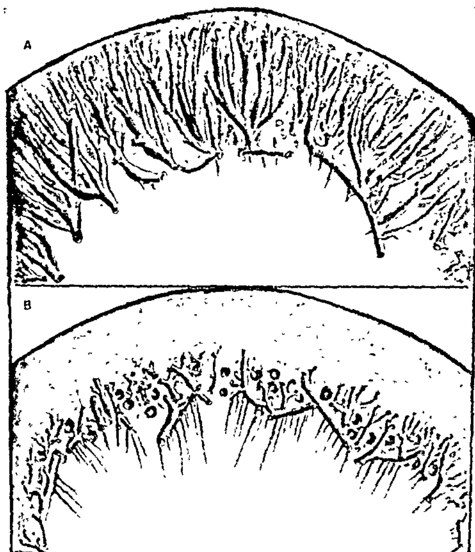



Fig. A. *Right kidney* of a rabbit showing the abundant normal distribution of radio opaque material within the diffusely patent cortical vessels and glomeruli.

Fig. B. *Left kidney* of the same rabbit in which the nerve plexus about the left renal artery was stimulated with faradic current. The result is an ischemic cortex with constriction of the peripheral segments of the interlobular arteries but with congestion of the juxtamedullary glomeruli and the vasa recta of the medulla. Trueta and his associates interpret this distribution of blood as indicative of a *bypass* of the cortical blood through the juxtamedullary glomeruli. Actually, the cortical (i.e., the outer cortical) glomeruli in human cases of cortical necrosis as well as hemoglobinuric nephrosis are commonly intensely congested in contrast to the above phenomenon in rabbits (compare plate 266B). (These drawings are based on radiomicrographs from Trueta's *Studies of the Renal Circulation*, Springfield, C. C Thomas, 1947, pp. 116–117.)

acute necrotizing glomerulonephritis (Dunn and Montgomery). Recent thrombi are generally present in the afferent arterioles, the interlobular arteries, and often in the arcuate arteries (plate 266C) These vessels, thus thrombosed, often show a fibrinoid necrosis of their walls A noteworthy feature of this fibrinoid necrosis is that it may involve an "upper" or *"outer" segment of an arcuate artery and spare* the "lower" or "inner" segment as if the cortex had been sharply swathed by a necrotizing agent leaving the juxtamedullary portion abruptly intact (plate 266C) The hemodynamics of this selective pattern of necrosis of the wall of a vessel is not clear even if Trueta's debatable concept is invoked.

Interstitial, glomerular and tubular hemorrhage may be marked. Foci of polymorphonuclear leukocytes, often more or less karyorrhectic, are commonly present just as they are in simple renal infarcts The medulla is hyperemic and is almost always spared, the medulla is usually intact in ordinary infarcts as well. As mentioned, the columns of Bertin containing cortical tissue may, of course, be involved

*Associated lesions*

Bilateral cortical necrosis may be associated with other renal lesions produced, however, by different pathogenetic mechanisms For example, the characteristic hydropic change of the tubular epithelium in diethylene glycol poisoning occurs with or without cortical necrosis (plate 120) Similarly, in pregnancy, cortical necrosis may be combined with acute membranous glomerulonephritis Such a combination in either instance is not to be interpreted as indicating the same pathogenesis for each of the component lesions

### *Pathogenesis*

Experimentally, bilateral cortical necrosis of the kidneys has been produced with pitressin (Byrom), adrenalin (Penner and Bernheim), staphylococcic toxin (De Navasquez), and daily intravenous administration of lithium carmine in rabbits for two to six days according to Gimenez Reyna. *There is a current trend to attribute* the cortical necrosis to shock but the production of the lesion in humans by various chemical agents indicates other mechanisms may play a part. Duff and More suggest a vascular hypersensitivity. Dunn and Montgomery postulate any one of three mechanisms are involved in cortical necrosis: (1) acute necrotizing glomerulonephritis, (2) ischemia and (3) veno-stasis secondary to renal vein thrombosis. Embolization, including fat embolization *and primary thrombosis of damaged renal* arteries, has had its advocates. Theories of renal vasomotor disturbances, despite their admittedly vague definition, have had most appeal (Scriver and Oertel; Ash).

Whatever the basic stimulus and its mode of application is, however, the concept of Trueta and his associates of this particular hemodynamic derangement seems most apt. They have vividly demonstrated in rabbits that crushing the muscles of an extremity, stimulating the sciatic nerve, or injecting pitressin is followed by ischemia of most of the cortex and hyperemia of the juxtamedullary glomeruli and medulla The result is symmetrical cortical necrosis of the kidneys In other words, with appropriate neural stimulation there is a diversion of blood from the outer to the inner cortical zone, leaving the outer zone relatively bloodless

Although the vagaries of the rabbit as an experimental animal are well known, the Trueta concept for the explanation of cortical necrosis seems the most fitting to date. However, the intense hyperemia of the outer cortical glomeruli *in human cases* constitutes a basic discrepancy in the application of the results in rabbits to humans.

### *Prognosis*

There is no positive evidence that patients may survive bilateral massive cortical necrosis A number of instances of such recovery are recorded but proof is lacking that the clinical picture of cortical necrosis was not simulated by some other serious renal lesion such as hemoglobinuric nephrosis or incomplete cortical ischemia falling short of necrosis Certainly one *does not see at autopsies* kidneys which appear to represent a healed stage of bilateral cortical necrosis

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FIG A *Fat embolism* as evidenced by clear spaces in glomeruli and peritubular capillaries The embolism followed extensive fractures of bones No glomerular reaction or tubular atrophy is present Renal function is rarely compromised by fat emboli (A F I P Acc 105694)

FIG B *Sudan III* stain of section in figure A, demonstrating the black lipid masses in glomerular and peritubular capillaries

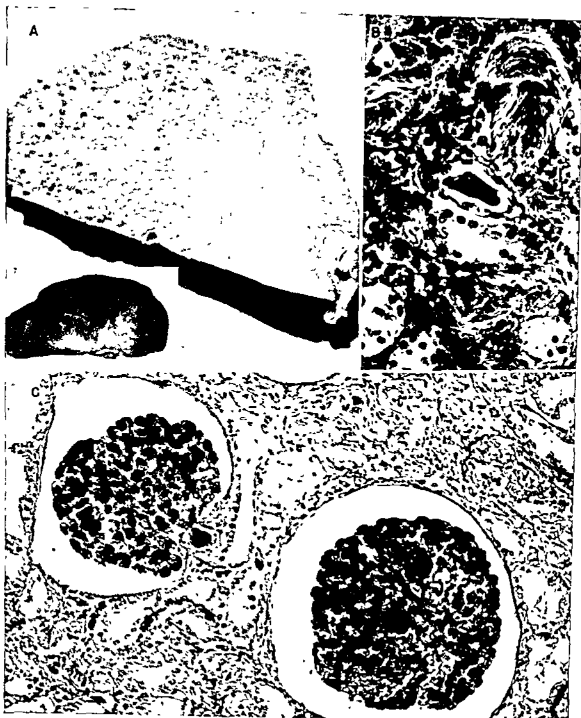



FIG A *Sickling in kidney* is characterized grossly by large congested glomeruli

FIG B *Sickled cells* in interlobular veins of kidney (formalin fixation) Sickling is not demonstrable in paraffin sections of Zenker fixed tissue

FIG C *Sickled cells in glomeruli* with extreme congestion due to compacted, sickled red blood cells Sickling of erythrocytes within the kidney may be responsible for severe hematuria

### Fat Emboli to Kidney

Very little has been added to our information on fat embolization to the kidney since the time of Vance's report in 1931. Fat embolism follows trauma to fat whether the fat be in bone marrow or in soft tissue more superficially Fat embolism results from fractures of bones, jarring of the skeleton, orthopedic operations, trauma to viscera and to subcutaneous and intermuscular fat, the intravenous injection or intraurethral instillation of various oils, volatile anesthetics, burns, sickle cell anemia and various poisons. The mode of death caused by fat embolism is (1) cerebral, or (2) pulmonary, depending on the extent of the capillary bed occluded and the location of vessels in the brain Microinfarcts with ring hemorrhages occur in the brain but not in the lungs Death may follow embolization in from a few seconds to several days, deaths delayed 25 days have been recorded (Warren)

The kidneys are rarely spared some degree of fat embolization in these cases There is a difference of opinion as to whether or not extensive lipid embolization causes renal dysfunction. The bulk of opinion is that the emboli do not produce significant renal embarrassment, contrary opinion has been recorded (Busse, Paul and Windholz) Possibly the dysfunction may be dependent on antecedent renal disease or the shock in such instances

The histologic picture of renal fat embolism, as observed in paraffin sections is characterized by focally dilated, bloodless, clear spaces within the glomerular capillaries The endothelial cells are flattened and the basement membrane stretched These spaces are occupied by fat as demonstrated with Sudan stains or osmic acid (plate 269). Lipid is present also in some of the peritubular capillaries The remarkable feature of the lesion is the total lack of reaction about the emboli. Lipiduria occurs commonly in these cases and may furnish the lead to the clinical diagnosis.

### Aneurysm of Renal Artery

Aneurysms of the renal artery occur rarely but may have grave consequences and therefore deserve a note As in other locations, the aneurysms are divided into (1) true and (2) false. The true aneurysm is caused by trauma to an intact artery or one weakened by arteriosclerosis, mycotic arteritis (plate 259A, B), periarteritis nodosa (plate 228B), syphilis, and congenital defects The false aneurysm is almost always the result of trauma with rupture of the artery and occlusion of the defect by blood clot The false aneurysm, which differs from the true aneurysm in that its wall is not made up of the three arterial coats but merely of organized clot, comprises about 15 per cent of the lesions

There are usually no symptoms of aneurysm of the renal artery until rupture occurs Occasionally abnormal pulsations, bruits, and murmurs are detected, and, in addition, there may be intermittent pain, recurrent hematuria, and even a palpable mass Hematuria may result from renal infarction or from perforation of the renal pelvis Radiologists may suggest the diagnosis on the basis of calcification ("ring shadow") of the wall of the aneurysm The calcified ring is incomplete at the point of origin of the aneurysm Such a density would have to be distinguished from renal calculi, *cholelithiasis, or calcified lymph nodes* Undiagnosed aneurysms have been ruptured inadvertently during operations in the region of the kidney Hypertension was present in 11 of the 56 cases of aneurysm of the renal artery reported since 1927, in 3 of these 11 patients, the hypertension was restored to a normal level after operation (Berneike and Pollack)

### References

*Arterial (Senile) Nephrosclerosis*

Kimmelstiel, P Glomerular changes in arteriosclerotic contraction of kidney Am J Path 11: 483–496, 1935

MacCallum, W G Glomerular changes in nephritis. Bull Johns Hopkins Hosp 55: 416–432, 1934

McGregor, L Histologic changes in the renal glomerulus in essential (primary) hypertension Am J Path 6 347–366, 1930

Staemmler, M Die Enstehung der arteriosklerotischen Schrumpfniere Beitr z path Anat u z. allg Path 85: 241–250, 1930

*Benign and Malignant Nephrosclerosis*


ABESHOUSE, B S *Hypertension* and unilateral renal disease, review of literature and report of 16 cases Surgery 9: 942, 10: 147, 1941

ALLEN, A C So-called intercapillary glomerulosclerosis lesions *associated with diabetes mellitus*, morphogenesis and significance Arch Path **32**: 33–51, 1941

ARONSON, S, AND SAMPSON, M Unilateral benign and malignant nephrosclerosis and cortical necrosis, associated with contralateral renal artery occlusion Arch Path **51**: 30–37, 1951

BAGGENSTOSS, A H, AND BARKER, N W. Unilateral renal atrophy associated with hypertension Arch Path **32**: 966–982, 1941

BELL, E T Renal Diseases Philadelphia, Lea and Febiger, 1946

BING, R J, AND ZUCKER, M B Formation of pressor amines in kidney Proc Soc Exp Biol & Med **46**: 343–347, 1941

BLACKFORD, J M, BOWERS, J M, AND BAKER, J W Follow-up study of hypertension J A M A **94**: 328–333, 1930

BLALOCK, A, AND LEVY, S E Studies on the etiology of hypertension Ann Surg **106**: 826–847, 1937

—— AND —— Gradual complete occlusion of the celiac axis, the superior and inferior mesenteric arteries with survival of animals, effects of ischemia on blood pressure Surgery **5**: 175–178, 1939

BOAS, E P, AND FINEBERG, M H Hypertension in *its relationship to mitral stenosis and aortic insufficiency* Am J M Sc **172**: 648–659, 1926

BRAASCH, W F Surgical kidney as an etiological factor in hypertension Canad M A J **46**: 9–15, *1942*

BRAUN-MENENDEZ, E, FASCIOLO, J C, LELOIR, L F, AND MUNOZ, T H Substance causing renal hypertension J Physiol **98**: 283–298, 1940

BRIGHT, R Reports of medical cases selected with a view of illustrating the symptoms and cure of diseases by a reference to morbid anatomy, Vol I London, Longman, Rees Orme, Brown and Green, 1827

BURKLAND, C E, GOODWIN, W E, AND LEADBETTER, W F The cure of hypertension by nephrectomy Surgery **28**. 67–70, 1950

BUTLER, A M Chronic pyelonephritis and arterial hypertension *J Clin Invest 16: 889–897, 1937.*

CANNADY, E W, AND O'HARE, J P A critical survey of the retinal lesions in chronic glomerular nephritis J A M A **103**: 6–10, 1934

*CARGILL*, W H The measurement of glomerular and [illegible]

CAS[illegible] [illegible] from hypertensive patients [illegible] ing of the [illegible] h **17**: 617–619, 1941

[illegible] AND —— The relation of vascular disease to the

hypertensive state, based on a study of renal bi*opsies from 100 hypertensive* patients *J.* A M A **121**: 1256–1261, 1943

CERQUA, S, AND SAMAAN, A. Cure of experimental renal hypertension Clin Sc. **4**: 113–118, 1939

COX, A J, AND DOCK, W.: *The capacity of the renal* vascular bed in hypertension J. Exper Med **74**: 167–175, 1941

DALEY, R M, UNGERLEIDER, H E, AND GUBNER, R S Prognosis in hypertension J A M A **121**: 383–389, 1943

DAVISON, G, AND BRILL, N Q. Essential hypertension and chronic hypertensive encephalopathy (clinico-pathologic study) Ann Int Med **12** 1766–1781, 1939

DAVISON, J Malignant hypertension associated with hydatid disease of the kidney J. Path and Bact **53**: 207–212, 1941.

DEMPSEY, W S The adrenal cortex in essential hypertension Arch Path **34**: 1031–1034, 1942

DEROW, H A, AND ALTSCHULE, M O The nature of malignant hypertension Ann Int. Med **14**: 1768–*1780, 1941*

FAHR, TH Maligne Nephrosclerose, in Die Pathologische Anatomie des Morbus Brightii Handbuch der speziellen pathologischen Anatomie und *Histologie, Henke, F., and Lubarsch, O Berlin*, J Springer, 1934, vol 6, pt 2, p 934

FISHBERG, A M The arteriolar lesions of glomerulonephritis Arch Int Med **40**. 80–97, 1927

—— Hypertension and Nephritis 4th Ed Philadelphia, Lea and Febiger, 1939

FOA, P P, FOA, N L, AND PEET, M M: Arteriolar lesions in hypertension a study of 350 consecutive cases treated surgically An estimation of the prognostic value of muscle biopsy J. Clin Invest **22**: 727–742, 1943

FREED, S C Psychic factors in development and treatment of obesity J A M A. **133**. 369–374, 1947

FREEMAN, G, AND HARTLEY, G, JR *Hypertension* in a patient with a solitary ischemic kidney J A M A **111**: 1159–1162, 1938

FRIEDMAN, B, MOSCHKOWITZ, L, AND MARRUS, J Unilateral renal disease and renal vascular changes in relation to hypertension in man J Urol **48**: 5–15, 1942

GASUL, B M, GLASSER, J M, AND GROSSMAN, A Extreme hypertension in a child cured by nephrectomy J A M A **139**. 305–307, 1949

GOLDBLATT, H Studies on experimental hypertension V *The pathogenesis of experimental* hypertension due to renal ischemia Ann Int Med **11**: 69–103, 1937

—— [illegible] mental hypertension VII The [illegible] hyperten- [illegible]

—— [illegible] rction and Pathogenesis of Experimental Hypertension

Spec. Pub N Y. Acad Science Vol III, 1946, pp 4-24
—— Renal origin of hypertension Physiol Rev 27: 120-165, 1947
——, Lynch, J, Hanzal, R F, and Summerville, W. W: Studies on experimental hypertension I The production of persistent elevation of systolic blood pressure by means of renal ischemia J Exp Med 59: 347-379, 1934
Goldring, W, and Chasis, H Hypertension and Hypertensive Disease New York, The Commonwealth Fund, 1944
Goodman, L Recurrent hypertensive cerebral thrombosis Arch Neur and Psych 62: 445-478, 1949
Grollman, A, Muirhead, E E, and Vanatta, J Role of the kidney in pathogenesis of hypertension as determined by a study of the effects of bilateral nephrectomy and other experimental procedures on the blood pressure of the dog Am J Physiol. 157: 21-30, 1949
Gull, W. W, and Sutton, H G On the pathology of the morbid state commonly called Bright's disease with contracted kidneys ("arterio capillary fibrosis") Med Chir Tr London 55: 273-329, 1872
Houssay, B A, and Taquini, A C Acción vasoconstrictora de la sangre venosa del riñon isquemiado Rev Soc argent de biol 14: 5-14, 1938
—— and —— Action vaso-constrictice du sang veineux du rein ischémié Compt rend Soc de biol 128 1125-1128, 1938
Jaffé, R H The vascular changes of the kidney in hypertension Am J M Sc 169: 88-102, 1925
Janeway, T C Nephritic hypertension, clinical and experimental studies Am J M Sc 145 625-656, 1913.
Kean, B H Blood pressure studies on West Indians and Panamanians living on the Isthmus of Panama Arch Int Med 68: 466-475, 1941
Keith, N M, Wagener, H P, and Kernohan, J W The syndrome of malignant hypertension Arch Int Med 41: 141-188 1928
Kennedy, R L J, and Barker, N W Malignant hypertension cure following nephrectomy Followup report of the case of a child Am J Dis Child 69: 160-162, 1945
Kimmelstiel, P, and Wilson, C Benign and malignant hypertension and nephrosclerosis, clinical and pathological study Am J Path 12. 45-82, 1936
Klemperer, P, and Otani, S "Malignant nephrosclerosis" (Fahr) Arch Path 11: 60-117, 1931
Leiter, L Unusual hypertensive disease, occlusion of renal arteries (Goldblatt) hypertension, anomalies of urinary tract J A M A 111: 507-510, 1938
Levy, R L, White, P D, Stroud, W D, and Hillman, C C. Sustained hypertension predisposing factors and causes of disability and death J A M A 135: 77-80, 1947.
Levy, S E, Light, R A, and Blalock, A Blood flow and oxygen consumption of kidney in experimental renal hypertension Am J Phys 122: 38-42, 1938
Lippmann Apoplexie, Encephalomalacie und Blutdruck Deutsch med Wchnschr 44: 907-909, 1918
Lohlein, M Zur Pathogenese der vascularen Schrumpfniere Med Klin 12. 741-743, 1916
MacMahon, H E, Close, H G, and Haas, G M: Cardiovascular renal changes associated with basophil adenoma of anterior lobe of pituitary (Cushing's syndrome) Am J Path 10. 177-191, 1934
Master, A M, Marks, H H, and Dack, S Hypertension in people over forty J A M A 121: 1251-1256, 1943
Moritz, A R, and Oldt, M R Arteriolar sclerosis in hypertensive and non hypertensive individuals Am J Path 13: 679-728, 1937
Moschcowitz, E Hypertension with minimal renal lesions J A M A 77. 1075, 1921
Muirhead, E E, Vanatta, J, and Grollman, A Hypertensive cardiovascular disease, an experimental study of tissue changes in bilaterally nephrectomized dogs Arch Path 48. 234-254, 1949
Murphy, F D, and Grill, J So-called malignant hypertension, a clinical and morphologic study Arch Int Med 46. 75-104, 1930
——, ——, Pessin, B, and Moxon, G F Essential (primary) hypertension a clinical and morphologic study of 375 cases Ann Int Med 6 31-53, 1932
Oppenheimer, B S, and Fishberg, A M Hypertensive encephalopathy Arch Int Med 41: 264-278, 1928
——, ——, Klemperer, P, and Moschkowitz, L: Evidence for the Goldblatt mechanism of hypertension in human pathology Tr A Am Physicians 54: 69-81, 1939
Oster, K A, and Sobotka, H Antipressor effects of orthoquinoid epinephrine derivatives in experimental hypertension in rat J Pharmacol & Exper Therap 78: 100-107, 1943
Page, I H A syndrome simulating diencephalic stimulation occurring in patients with essential hypertension Am J M Sc 190: 9-14, 1935
—— Production of persistent arterial hypertension by cellophane perinephritis J A M A 113: 2046-2048, 1939
Paullin, J E, Bowcock, H M, and Wood, R H Complications of hypertension Am Heart J 2: 613-617, 1927
Rinehart, T F, Williams, O O, and Cappeller, W S Adenomatous hyperplasia of the adrenal cortex with essential hypertension Arch Path 32: 169-177, 1941.

ROBINSON, S C, AND BRUCER, M Range of normal blood pressure, statistical and clinical study of 11,383 *persons Arch Int Med 64: 409–444, 1939*
——, ——, AND MASS, J Hypertension and obesity, statistical and clinical study of 10,883 individuals J Lab & Clin Med 25: 807–822, 1940
SAPEIKA, N Adrenal cortex and hypertension Arch. Int Med 82: 263–309, 1948
SAPHIR, O, AND BALLINGER, J *Hypertension (Goldblatt)* and unilateral malignant nephrosclerosis Arch Int Med 66. 641–650, 1940
SCHFINKER, I M Hypertensive cerebral swelling, a characteristic clinico-pathologic syndrome Ann Int Med 28: 630–641, 1948
SCHRODER, J C, YOUNG, J M, AND PAGE, I H Pyelograms in patients with essential and malignant hypertension Am J M Sc 205: 505–514, 1943
SCHÜRMANN, P, AND MACMAHON, H E Die maligne Nephrosklerose zugleich ein Beitrag zur Frage *der Bedeutung der Blutgewebsschranke* Virchow's Arch f path Anat 291: 47–218, 1933
SCHWARTZ, N H, AND GROSS, S Unilateral malignant nephrosclerosis J Urol 62. 426–435, 1949
SELYE, H Textbook of Endocrinology 2nd Ed Montreal, Acta Endocrinologica, Inc, 1949
SENSENBACH, W W Effects of unilateral nephrectomy in treatment of hypertension, and evaluation Arch Int Med 73: 123–130, 1944
SWEENEY, J S, AND PACE, J M Hypertension caused by unilateral kidney disease (a follow-up report) Ann Int Med 29: 370–374, 1948
TIGERSTEDT, R, AND BERGMAN, P G Niere und Kreislauf Skandin Arch f Physiol 8. 223–271, 1898
VICTOR, J Discussion of Goldblatt, H, Introductory Lecture on the Production and Pathogenesis of Experimental Hypertension Spec Pub N Y Acad Science, Vol III, 1946, pp 24–26
VOLINI, I F, AND FLAXMAN, N The effects of non*specific operations on essential hypertension* J. A M A 112. 2126–2128, 1939
WALKER, W J Obesity as a problem in preventive medicine U S Armed Forces M J 1: 393–402, 1950
WATERS, L L Changes in the coronary and visceral arterioles of dogs following large doses of adrenalin Am J Path (Sc Proc) 26. 687–699, 1950
WETHERBY, M Comparison of blood pressure in men and women, statistical study of 5,540 individuals. Ann Int Med 6: 754–770, 1932
WILSON, C, AND BYROM, F B Renal changes in malignant hypertension, experimental evidence Lancet 1: 136–139, 1939
YUILE, C L Obstructive lesions of the main renal artery in relation to hypertension Am J M Sc 207: 394–404, 1944

*Periarteritis Nodosa*

ADDIS, T Glomerular Nephritis New York, Macmillan, 1948
ARKIN, A · A clinical and pathological study of periarteritis nodosa; report of 5 cases, one histologically healed. Am J. Path 6: 401–426, 1930
BENNETT, G A., AND LEVINE, S A Two cases of periarteritis nodosa, one with unusual manifestations (meningeal form). Am J M Sc 177: 853–859, 1929
FRIEDBERG, C. K, AND GROSS, L Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease, with note on abdominal rheumatism Arch Int Med 54. 170–198, 1934
GERLACH, W: Ueber Periarteritis nodosa Klin Wchnschr 1: 467–470, 1922
GRUBER, G B Zur Frage des Periarteritis nodosa Virchow's Arch f path Anat 258: 441–501, 1925
HELPERN, M, AND TRUBEK, M Necrotizing arteritis and subacute glomerulonephritis in gonococcic endocarditis, toxic origin of periarteritis nodosa Arch Path 15: 35–50, 1933
KRUPP, M A Urinary sediment in visceral angiitis *(periarteritis nodosa) lupus erythematosus, Lib*man-Sacks "disease"), quantitative studies Arch Int Med 71: 54–61, 1943
KUSSMAUL, A., AND MAIER, R Ueber eine bischer nicht beschriebene eigentumliche Arterienerkrankung (Periarteritis nodosa) Deutsches Arch f Klin Med 1: 484–518, 1865–6
POWELL, R E, AND PRITCHARD, J E Periarteritis nodosa, with report of a case involving one kidney Brit. J Urol 4: 317–327, 1932
RALSTON, D E., AND KVALE, W F Renal lesions of periarteritis nodosa Proc Staff Meetings Mayo Clinic 24: 18–27, 1949.
RICH, A R · The role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy Bull Johns Hopkins Hosp 71: 123–140, 1942
ROTHSTEIN, J L, AND WELT, S Periarteritis nodosa in infancy and childhood Am J Dis Child 45: 1277–1308, 1933
SPIEGEL, R *Clinical aspects of periarteritis* nodosa Arch Int Med 58. 993–1040, 1936
STRONG, G F Periarteritis nodosa with report of case Canad M A J 19: 534–546, 1928
WEYER, G K, AND PERRY, I H Periarteritis nodosa report *of case with fatal perirenal* hemorrhage J A M A 104. 1390–1395, 1935

*Diabetic Glomerulosclerosis*

ALLEN, A C So-called intercapillary glomerulosclerosis—a lesion associated with diabetes mellitus morphogenesis and significance *Arch* Path 32: 33–51, 1941
ANSON, L J Intercapillary glomerulosclerosis South M J 31: 1272–1275, 1938
BELL, E T Renal Diseases Philadelphia, Lea and Febiger, 1947.
... *of glomerular le-*
781–796, 1942
... PAGE, I H

Functional patterns in renal disease Ann Int Med 28 560–582, 1948
DEROW, H A, ALTSCHULE, M O, AND SCHLESINGER, M J Syndrome of diabetes mellitus, hypertension and nephrosis, clinical and pathologic study of a case New England J Med 221 1012–1015, 1939
——, AND SCHLESINGER, M J The evolution of intercapillary glomerulosclerosis New England J Med 241 7–12, 1949
GOODOF, I I Intercapillary glomerulosclerosis Ann Int Med 22, 373–381, 1945
HENDERSON, L L, SPRAGUE, R G, AND WAGENER, H P Intercapillary glomerulosclerosis Am J Med 3: 131–144, 1947
HERBUT, P A Intercapillary glomerulosclerosis Arch Path 31· 501–507, 1941
HORN, R C, JR, AND SMETANA, H Intercapillary glomerulosclerosis Am J Path 18 93–99, 1942
KIMMELSTIEL, P, AND WILSON, C Intercapillary lesions in the glomeruli of the kidney Am J Path 12. 83–98, 1936
LAIPPLY, T C, EITZEN, O, AND DUTRA, F R Intercapillary glomerulosclerosis Arch Int Med 74 354–364, 1944
LUKENS, F D W, AND DOHAN, F C Experimental pituitary diabetes of five years' duration with glomerulosclerosis Arch Path 41 19–24, 1946
MIRSKY, I A, AND NELSON, N Significance of glycosuria Arch Int Med 71. 827–835, 1943
NEWBURGER, R A, AND PETERS, J P Intercapillary glomerulosclerosis A syndrome of diabetes, hypertension and albuminuria Arch Int Med 64· 1252–1264, 1939
OLIVER, J When is a kidney not a kidney? J Urol 63· 373–402, 1950
RIFKIN, H, PARKER, J G, POLIN, E B, BERKMAN, J I, AND SPIRO, D Diabetic glomerulosclerosis, clinical and pathologic observations with special reference to doubly refractile fatty cells and casts in the urine Medicine 27 429–456, 1948
ROBBINS, S L Renal lesions in diabetes mellitus Bull New England M Center 10 78–83, 1948
SIEGEL, S, AND ALLEN, A C Intercapillary glomerulosclerosis (Kimmelstiel-Wilson) and nephrotic syndrome in diabetes mellitus Am J M Sc 201 516–528, 1941
WARREN, S Pathology of Diabetes Mellitus Philadelphia, Lea and Febiger, 1938, p 87

*Amyloidosis*

BELL, E T Amyloid disease of kidneys Am J Path 9 185–204, 1933
BENNHOLD, H Ueber die Ausscheidung intravenos verschiedensten Erkrankungen insbesondere bei Amyloidosis Deutsch Arch f Klin Med 142. 32–46, 1923
FISHBERG, A M Hypertension and Nephritis Philadelphia, Lea and Febiger, 1939, p 415
GEILL, T Klinische Untersuchungen uber Albumin und Globulin im Blut und im Harn bei Nierenkranken Ztschr f Klin Med 110 334–381, 1929
JAFFÉ, R H Amyloidosis produced by injections of proteins Arch Path 1· 25–36, 1926
—— Experimental amyloidosis in mice, effect of different forms of diet Arch Path 2 149–160, 1926
KRAWKOW, N P De la dégénérescence amyloide et des altérations cirrhotiques provoquées expérimentalement chez les animaux Arch de méd expér et d'anat -path, Paris 8· 106–133, 1896
KUCZYNSKI, M H Neue Beitrage zur Lehre vom Amyloid Klin Wchnschr, Berl 2 727–730, 1923
LEARD, S E, AND JAQUES, W E Amyloid disease with hypertension, report of a case and review of the literature New England J Med 242· 891–894, 1950
LINDER, G C, MAXWELL, J, AND GREEN, F H K Clinical, pathological and biochemical study of amyloid nephrosis Arch Dis Child 2 220–230, 1927
REINMANN, H A Recovery from amyloidosis J A M A 104 1070–1071, 1935

*Generalized Arteriolo Capillary Thrombonecrosis*

ADAMS, R D, CAMMERMEYER, J, AND FITZGERALD, P J The neuropathological aspects of thrombocytic acroangiothrombosis A clinico anatomical study of generalized platelet thrombosis J Neurol, Neurosurg, & Psychiat 11 27–43, 1948
ALLEN, A C, AND SIROTA, J H Morphogenesis and significance of degenerative verrucal endocardiosis (terminal endocarditis, endocarditis simplex, nonbacterial thrombotic endocarditis) Am J Path 20 1025–1056, 1944
——, AND SPITZ, S Comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases Am J Path 21· 603–681, 1945
BAEHR, G, KLEMPERER, P, AND SCHIFRIN, A Acute febrile anemia and thrombocytopenic purpura with diffuse platelet thromboses of capillaries and arterioles Trans A Am Phys 51 43–58, 1936
ENGEL, G L, SCHEINKER, I M, AND HUMPHREY, D C Acute febrile anemia and thrombocytopenic purpura with vasothrombosis Ann Int Med 26 919–933, 1947
FITZGERALD, P J, AUERBACH, O, AND FRAME, E Thrombocytic acroangiothrombosis (platelet thrombosis of the capillaries, arterioles and venules) Blood 2 519–541, 1947
GORE, I Disseminated arteriolar and capillary thrombosis A morphologic study of its histogenesis Am J Path 26 155–175, 1950
MOSCHCOWITZ, E An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries An undescribed disease Arch Int Med 36 89–93, 1925

*Shock*

ASH, J E, AND SPITZ, S Pathology of Tropical Diseases An Atlas Philadelphia, Saunders, 1945

Koletsky, S, and Gustafson, G E Effects of temporary cessation of renal blood flow in rats J Clin Invest 26: 1072-1078, 1947

Trueta, J, Barclay, A E, Daniel, D M, Franklin, K F, and Pritchard, M M L Studies of the Renal Circulation Springfield, Ill, C. C Thomas, 1947

Van Slyke, D D Effects of shock on the kidney Ann Int Med 28. 701-722, 1948

*Renal Infarcts*

Aschner, P W Thrombosis and thrombophlebitis of the renal vein J Urol 17. 309-327, 1927

Barenberg, L H, Greenstein, N M, Levy, W, and Rosenbluth, S B Renal thrombosis with *infarction complicating diarrhea of the newborn*, summary of 5 cases Am J Dis Child 62: 362-372, 1941

Bell, E T Renal Diseases Philadelphia, Lea and Febiger, 1946

Blake, W D, Wégria, R, Keating, R P, and Ward, H P Effect of increased renal venous pressure on renal function Am J Physiol 157. 1-13, 1949

Cabot Case #36032 Clinico-pathologic conference, Massachusetts General Hospital New England J. Med 242· 100-104, 1950

Campbell, K N, Harris, B M, and Coller, F A Follow-up study of patients with thromboangiitis obliterans (Buerger's disease) Surgery 26: 1003-1013, 1950

Campbell, M F, and Matthews, W F. Renal thrombosis in infancy J Pediat 20· 604-615, 1942

Danhiez, P Les grands infarctus renaux J d'urol 23: 481-495, 1927

Derow, H A, Schlesinger, M J, and Savitz, H A Chronic progressive occlusion of the inferior vena cava and the renal and portal veins with clinical picture of nephrotic syndrome. Arch Int Med 63: 626-647, 1939

Fuhr, K T Über totale Nekrose beider Nieren nach Thrombose der Nierenvenen Inaug diss., Giessen, 1903

Goodwin, W E, Alston, E F, and Semans, J H Hematuria and sickle cell disease, unexplained gross unilateral renal hematuria in Negroes coincident with the blood sickling trait J Urol 79-96, 1950

Grüneberg, B Nierenvene thrombose linkerseits Munchen med Wchnschr 79: 1054, 1932

Heller, S Thrombose der beiderseitigen Vena renalis bei einem Neugeborenen Zentralbl f. Gynäk 47: 1897-1899, 1923.

Hirshberg, H. A, and Soll, S N Renal infarction of traumatic origin J A M A. 119. 1088, 1942

Hoxie, H J, and Coggin, C B Renal infarction, statistical study of 205 cases and detailed report of unusual case Arch Int Med 65: 587-594, 1940

Loomis, D, and Jett-Jackson, C E Plastic studies in abnormal renal architecture; investigation of circulation in infarcts of kidney. Arch Path 33: 735-769, 1942

Marshall, S., and Whapham, E Case of bilateral renal infarction in a newly born infant Lancet 2. 428-429, 1936

Melick, W. F., and Vitt, A E · Thrombosis of the renal vein J Urol 51: 587-596, 1944

Penner, A, and Bernheim, A I Acute ischemic necrosis of the kidney, clinico-pathologic and experimental study Arch Path. 30: 465-480, 1940

Prinzmetal, M, Hiatt, N., and Trageman, L J · Hypertension in a patient with bilateral renal infarction, clinical confirmation of experiments in animals J A M A 118: 44-46, 1942

Regan, F C, and Crabtree, E G. Renal infarction, clinical and possible surgical entity J Urol 59: 981-1018, 1948

Sharp, R F, and Green, M M. Diagnostic and therapeutic considerations in renal aneurysm with a report of two additional cases J Urol 64· 214-223, 1950.

Shea, J D, Schwartz, J W., and Kobilak, R. E Thrombosis of left renal artery with hypertension, case report J Urol 59: 302-306, 1948

Stegeman, W Renal vessel thromboses Urol & Cutan Rev 52: 710-712, 1948

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Ash, J E Bilateral cortical necrosis of the kidneys (angioneurotic anemia) Am J. M Sc 185: 71-86, 1933

Byrom, F B Morbid effects of vasopressin on the organs and vessels of rats J. Path & Bact 45: 1-16, 1937

De Navasquez, S Experimental symmetrical cortical necrosis of the kidneys produced by staphylococcus toxin, a study of the morbid anatomy and associated circulatory and biochemical changes J Path & Bact 46: 47-65, 1938

Doniach, I, and Walker, A H C. Combined anterior pituitary necrosis and bilateral cortical necrosis of the kidneys, following concealed accidental hemorrhage J Obstet & Gynaec Brit Emp 53: 140-147, 1946

Duff, G L, and More, R H: Bilateral cortical necrosis of kidneys Am J M Sc 201: 428-450, 1941

Dunn, J S, and Montgomery, G L Acute necrotizing glomerulonephritis J. Path & Bact 52: 1-16, 1941

Gimenez Reyna, F.. Toxic effect of intravenous injections of lithium carmine, relation to total necrosis of kidneys and suprarenal cortex Beitr z path Anat u z allg Path 97: 261-288, 1936

Grasby, E D Y Combined anterior pituitary necrosis and symmetrical cortical necrosis of kidneys following accidental hemorrhage J Obst & Gynaec Brit Emp 54: 203-212, 1947.

Hugin, W Über Nierenrinden und Hypophysen vor-

derlappennekrose bei Gravidität, ein Beitrag zur Morphologie der Eklampsie Gynaecologia 121 269–287, 1946
Lungano, M Necrosi bilaterale del rene per embolia dell'arteria renale Riinasc med 4: 372-375, 1927
Jubel-Rénoy, E De l'anurie précoce scarlatineuse Arch gén d méd 1: 385–410, 1886
Penner, A, and Bernheim, A I Acute ischemic necrosis of the kidney, clinico pathologic and experimental study Arch Path 30: 465–480, 1940
Scriver, W de M, and Oertel, H J Necrotic sequestration of the kidneys in pregnancy (symmetrical cortical necrosis), clinical and anatomicpathogenetic study J Path & Bact 33. 1071–1094, 1930
Sheldon, W H, and Hertig, A T Bilateral necrosis of the kidney, report of 2 cases Arch Path 34: 866–874, 1942
Trueta, J, Barclay, A E, Daniel, P M, Franklin, K J, and Prichard, M M L Studies of the Renal Circulation Springfield, Ill, C C Thomas, 1947

*Fat Embolization*

Busse, O Fettembolie, Aerztl Sachverst -Ztg, Berlin 7. 389–392, 1901
Paul, F, and Windholz, F Experimentelle Studien uber die Fettembolie und den durch sie verursachten Tod Mitt Grenzgeb Med Chir 38. 614–651, 1924–25
Vance, B M The significance of fat embolism Arch Surg 23: 426–465, 1931
Warren, S Fat embolism Am J Path 22: 69–87, 1946

*Aneurysm of the Renal Artery*

Berneike, R R, and Pollack, H M True renal artery aneurysm, report of a case New England J Med 243 12–14, 1950
Mathé, C P Aneurysm of renal artery, report of five cases, one treated by resection of aneurysmal sac without sacrificing kidney J Urol 60: 543–551, 1948

olitsky, S., and Gustafson, G. E.: Effects of temporary cessation of renal blood flow in rats. J. Clin. Invest. 26: 1072-1078, 1947.
uteya, J., Barclay, A. E., Daniel, D. M., Franklin, K. F., and Prichard, M. M. L.: Studies of the Renal Circulation. Springfield, Ill.: C. C Thomas, 1947.
an Slyke, D. D.: Effects of shock on the kidney. Ann. Int. Med. 28: 701-722, 1948.

*Renal Infarcts*

ckner, P. W.: Thrombosis and thrombophlebitis of the renal vein. J. Urol. 17: 219-227, 1927.
arenberg, L. H., Greenstein, N. M., Levy, W., and Rosenbluth, S. B.: Renal thrombosis with infarction complicating diarrhea of the newborn; summary of 5 cases. Am. J. Dis. Child. 62: 362-372, 1941.
ell, E. T.: Renal Diseases. Philadelphia, Lea and Febiger, 1946.
lake, W. D., Wégria, R., Keating, R. P., and Ward, H. P.: Effect of increased renal venous pressure on renal function. Am. J. Physiol. 157: 1-13, 1949.
abot Case #36022: Clinico-pathologic conference. Massachusetts General Hospital. New England J. Med. 242: 100-104, 1950.
ampbell, K. N., Harris, B. M., and Coller, F. A.: Follow-up study of patients with thromboangiitis obliterans (Buerger's disease). Surgery 28: 1003-1013, 1950.
ampbell, M. F., and Matthews, W. F.: Renal thrombosis in infancy. J. Pediat. 20: 604-615, 1942.
anelli, P.: Les grands infarctus renaux. J. d'urol. 23: 481-495, 1927.
ebow, H. A., Schlesinger, M. J., and Savitz, H. A.: Chronic progressive occlusion of the inferior vena cava and the renal and portal veins with clinical picture of nephrotic syndrome. Arch. Int. Med. 63: 620-647, 1939.
the, K. T.: Über totale Nekrose beider Nieren nach Thrombose der Nierenvenen. Inaug. diss., Giessen, 1913.
oodwin, W. E., Alston, E. F., and Semans, J. H.: Hematuria and sickle cell disease; unexplained gross unilateral renal hematuria in Negroes coincident with the blood sickling trait. J. Urol. 79-96, 1950.
etznerberg, B.: Nierenvene thrombose linkerseits. München. med. Wchnschr. 79: 1054, 1932.
eller, S.: Thrombose der beiderseitigen Vena renalis bei einem Neugeborenen. Zentralbl. f. Gynäk. 47: 1897-1899, 1923.
irshberg, H. A., and Soll, S. N.: Renal infarction of traumatic origin. J. A. M. A. 119: 1088, 1942.
oxie, H. J., and Coggin, C. B.: Renal infarction; statistical study of 205 cases and detailed report of unusual case. Arch. Int. Med. 65: 587-594, 1940.
oomis, D., and Jett-Jackson, C. E.: Plastic studies in abnormal renal architecture; investigation of circulation in infarcts of kidney. Arch. Path. 33: 735-759, 1942.
Marshall, S., and Whapham, E.: Case of bilateral renal infarction in a newly born infant. Lancet 2: 428-429, 1935.
Melick, W. F., and Vitt, A. E.: Thrombosis of the renal vein. J. Urol. 51: 587-597, 1944.
Pennie, A., and Bierstein, A. L.: Acute ischemic necrosis of the kidney; clinico-pathologic and experimental study. Arch. Path. 30: 475-489, 1940.
Prinzmetal, M., Hiatt, N., and Tragerman, L. J.: Hypertension in a patient with bilateral renal infarction; clinical confirmation of experiments in animals. J. A. M. A. 118: 44-46, 1942.
Regan, F. C., and Crabtree, E. G.: Renal infarction: clinical and possible surgical entity. J. Urol. 59: 981-1018, 1948.
Sharp, R. F., and Green, M. M.: Diagnostic and therapeutic considerations in renal aneurysm with a report of two additional cases. J. Urol. 64: 214-223, 1950.
Shea, J. D., Schwartz, J. W., and Koehlak, R. E.: Thrombosis of left renal artery with hypertension: case report. J. Urol. 59: 372-376, 1948.
Stechman, W.: Renal vessel thromboses. Urol. & Cutan. Rev. 52: 710-712, 1948.

*Bilateral Cortical Necrosis*

Ash, J. E.: Bilateral cortical necrosis of the kidneys (angioneurotic anemia). Am. J. M. Sc. 185: 71-86, 1933.
Byrom, F. B.: Morbid effects of vasopressin on the organs and vessels of rats. J. Path. & Bact. 45: 1-16, 1937.
De Navasquez, S.: Experimental symmetrical cortical necrosis of the kidneys produced by staphylococcus toxin; a study of the morbid anatomy and associated circulatory and biochemical changes. J. Path. & Bact. 46: 47-65, 1938.
Doniach, I., and Walker, A. H. C.: Combined anterior pituitary necrosis and bilateral cortical necrosis of the kidneys, following concealed accidental hemorrhage. J. Obstet. & Gynaec. Brit. Emp. 53: 140-147, 1946.
Duff, G. L., and More, R. H.: Bilateral cortical necrosis of kidneys. Am. J. M. Sc. 201: 428-450, 1941.
Dunn, J. S., and Montgomery, G. L.: Acute necrotizing glomerulonephritis. J. Path. & Bact. 52: 1-16, 1941.
Gimenez Reyna, F.: Toxic effect of intravenous injections of lithium carmine; relation to total necrosis of kidneys and suprarenal cortex. Beitr. z. path. Anat. u. z. allg. Path. 97: 261-288, 1936.
Grasby, E. D. Y.: Combined anterior pituitary necrosis and symmetrical cortical necrosis of kidneys following accidental hemorrhage. J. Obst. & Gynaec. Brit. Emp. 54: 203-212, 1947.
Hugin, W.: Über Nierenrinden und Hypophysen vor-

derlappennekrose bei Gravidität, ein Beitrag zur Morphologie der Eklampsie Gynaecologia 121: 269-287, 1946
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JUHEL RÉNOY, E De l'anurie précoce scarlatineuse Arch gén d méd 1: 385-410, 1886
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SHELDON, W H, AND HERTIG, A T Bilateral necrosis of the kidney, report of 2 cases Arch Path 34: 866-874, 1942
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*Fat Embolization*

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VANCE, B M The significance of fat embolism Arch Surg 23 426-465, 1931
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MATHÉ, C P Aneurysm of renal artery, report of five cases, one treated by resection of aneurysmal sac without sacrificing kidney J Urol 60: 543-551, 1948

KOLETSKY, S, AND GUSTAFSON, G E Effects of temporary cessation of renal blood flow in rats J Clin Invest 26: 1072–1078, 1947

TRUETA, J, BARCLAY, A E, DANIEL, D M, FRANKLIN, K F, AND PRITCHARD, M M L Studies of the Renal Circulation Springfield, Ill, C C Thomas, 1947

VAN SLYKE, D D Effects of shock on the kidney Ann Int Med 28: 701–722, 1948

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BARENBERG, L H, GREENSTEIN, N M, LEVY, W, AND ROSENBLUTH, S B Renal thrombosis with infarction complicating diarrhea of the newborn, summary of 5 cases Am J Dis Child 62: 362–372, 1941

BELL, E T Renal Diseases Philadelphia, Lea and Febiger, 1946

BLAKE, W D, WÉGRIA, R, KEATING, R P, AND WARD, H P Effect of increased renal venous pressure on renal function Am J Physiol 157: 1–13, 1949

Cabot Case #36032 Clinico-pathologic conference, Massachusetts General Hospital New England J. Med 242 100–104, 1950

CAMPBELL, K N, HARRIS, B M, AND COLLER, F A Follow-up study of patients with thromboangiitis obliterans (Buerger's disease) Surgery 26: 1003–1013, 1950

CAMPBELL, M F, AND MATTHEWS, W F Renal thrombosis in infancy J Pediat 20: 604–615, 1942

DANHIEZ, P Les grands infarctus renaux J d'urol 23: 481–495, 1927

DEROW, H A, SCHLESINGER, M J, AND SAVITZ, H A Chronic progressive occlusion of the inferior vena cava and the renal and portal veins with clinical picture of nephrotic syndrome Arch Int Med 63: 626–647, 1939

FUHR, K. T Über totale Nekrose beider Nieren nach Thrombose der Nierenvenen Inaug diss, Giessen, 1903

GOODWIN, W E, ALSTON, E F, AND SEMANS, J H. Hematuria and sickle cell disease, unexplained gross unilateral renal hematuria in Negroes coincident with the blood sickling trait J Urol 79–96, 1950

GRÜNEBERG, B Nierenvene thrombose linkerseits München med Wchnschr 79: 1054, 1932

HELLER, S. Thrombose der beiderseitigen Vena renalis bei einem Neugeborenen Zentralbl f. Gynäk 47: 1897–1899, 1923

HIRSHBERG, H A, AND SOLL, S N Renal infarction of traumatic origin. J A M A 119. 1088, 1942

HOXIE, H J, AND COGGIN, C B · Renal infarction, statistical study of 205 cases and detailed report of unusual case Arch Int Med 65: 587–594, 1940

LOOMIS, D, AND JETT-JACKSON, C E · Plastic studies in abnormal renal architecture, investigation of circulation in infarcts of kidney. Arch Path 33: 735–769, 1942

MARSHALL, S, AND WHAPHAM, E Case of bilateral renal infarction in a newly born infant Lancet 2: 428–429, 1936

MELICK, W F, AND VITT, A. E · Thrombosis of the renal vein J Urol 51: 587–596, 1944

PENNER, A, AND BERNHEIM, A I Acute ischemic necrosis of the kidney; clinico-pathologic and experimental study. Arch Path 30: 465–480, 1940

PRINZMETAL, M, HIATT, N., AND TRAGERMAN, L. J Hypertension in a patient with bilateral renal infarction, clinical confirmation of experiments in animals J A M A 118: 44–46, 1942

REGAN, F C, AND CRABTREE, E G · Renal infarction, clinical and possible surgical entity J Urol 59: 981–1018, 1948

SHARP, R F, AND GREEN, M M Diagnostic and therapeutic considerations in renal aneurysm with a report of two additional cases J Urol 64: 214–223, 1950

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GIMENEZ REYNA, F Toxic effect of intravenous injections of lithium carmine, relation to total necrosis of kidneys and suprarenal cortex Beitr z path Anat u z allg Path 97: 261–288, 1936

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HEGIN, W Über Nierenrinden und Hypophysen vor-

derlappennekrose bei Gravidität; ein Beitrag zur Morphologie der Eklampsie Gynaecologia 121: 269–287, 1946

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JUHEL-RÉNOY, E De l'anurie précoce scarlatineuse Arch gén. d méd 1: 385–410, 1886

PENNER, A, AND BERNHEIM, A I Acute ischemic necrosis of the kidney, clinico pathologic and experimental study Arch Path 30, 465–480 1940

SCRIVER, W. DE M, AND OERTEL, H J Necrotic sequestration of the kidneys in pregnancy (symmetrical cortical necrosis), clinical and anatomic-pathogenetic study, J Path & Bact 33. 1071–1094, 1930

SHELDON, W. H, AND HERTIG, A T Bilateral necrosis of the kidney, report of 2 cases Arch Path 34: 866–874, 1942

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# 14. Tumors of the Kidney

### *Introduction*

THERE are many varieties of renal tumors, but it is fair to state that, except for the parenchymatous carcinomas, the pelvic papillomas and carcinomas, and the Wilms' tumors, the others are either oddities, or relatively insignificant from a clinical point of view. Grossly discernible benign tumors of the kidney are found in about 5 per cent of kidneys. Renal cancers constitute approximately 1.3 per cent of all cancers, the incidence is higher in males than in females (Macdonald).

### *Clinical features*

The cardinal signs and symptoms of a renal tumor are, in order of frequency: (1) painless hematuria, (2) local pain unrelated to hematuria, and (3) a palpable mass, the reversal of this order of frequency holds in the case of Wilms' tumors. In addition, compression, elongation, dilatation, distortion or filling defect of renal calyces or pelvis as revealed by intravenous and especially by retrograde pyelography, particularly if associated with calcium flecks in the mass, constitute confirmatory evidence. All of this evidence may be produced by benign or malignant renal tumors, or by retroperitoneal, extrarenal tumors which have encroached on the kidney. On the other hand, benign or malignant tumors of the kidney may remain clinically silent, and in the case of the latter, may nevertheless give rise to extensive metastases. Renal tumors may be simulated by mesenteric cysts, neoplasms of the sigmoid and descending colon, pancreatic masses, splenomegaly, Reidel's lobe of the liver, enlargement of regional lymph nodes, and cysts or tumors of the female internal genital organs. In any case of unexplained hematuria, the possibility of renal tumor must be ruled out. Other general signs and symptoms that may be present include fever, chills, anemia, weight loss, anorexia, leukocytosis, and varicocele secondary to involvement of the spermatic or ovarian vein, particularly on the left side where they enter the renal vein (Bonnecarrere). Malignant tumors of the kidney are about twice as common in males as in females, and, exclusive of the Wilms' tumors, are most common in the sixth and seventh decades. They occur with equal frequency in either kidney. Bilateral parenchymal renal malignant neoplasms are rare. Occasionally, metastases are taken for bilaterality.

Renal tumors may occasionally be associated with the development of hypertension and with its regression after nephrectomy. The problem of causal relation is the same as in other types of unilateral renal disease and is equally unsettled. In the case of the renal tumors, it is to be remembered that many of them occur at an age when hypertension is common.

Although benign and malignant tumors occur in anomalous kidneys, there is no statistically significant evidence of their predisposition to neoplastic growth.

### *Diagnosis from exfoliated cells*

Recently, the diagnosis of renal neoplasms from examination of smears and blocks of the urinary sediment for neoplastic cells has been advocated (Foot and Papanicolaou). Plate 293B, C, and D are examples of such sediments. However, this procedure requires the keenest kind of evaluation and is fraught with hazards. One such pitfall is the mistaking of regenerating or otherwise altered parenchymal tubular cells for cancer cells (plate 309B). Another error may result from pushing the cells of a bladder cancer up into the ureter by means of a catheter with the consequent diagnosis of renal cancer and subsequent nephrectomy (Staff of St. Vincent's). A frank evaluation of the problem is presented by *Bunge and Krausbaar* who report two cases in which normal kidneys were found




FIG A *Tubular cortical adenomas* located just beneath the capsule are indicated as small grey nodules (arrow) These nodules are grossly similar to small adrenal rests, lipomas, fibromas, leiomyomas or angiomyolipomas

FIG B *Tubular papillary cystadenoma*, made up of papillary projections, as if the tubular epithelium had undergone epithelial hyperplasia The transition from the normal tubules at the periphery is illustrated

FIG C *Minute tubular cystadenoma*, away from the capsule and deep in the cortex, clearly suggesting origin from epithelium of distal tubules in this instance Microcysts, as shown here, are also frequently present

FIG D *Papillary tubular adenoma* with interstitial deposits of lipid histiocytes, common in these tumors and their malignant counterpart

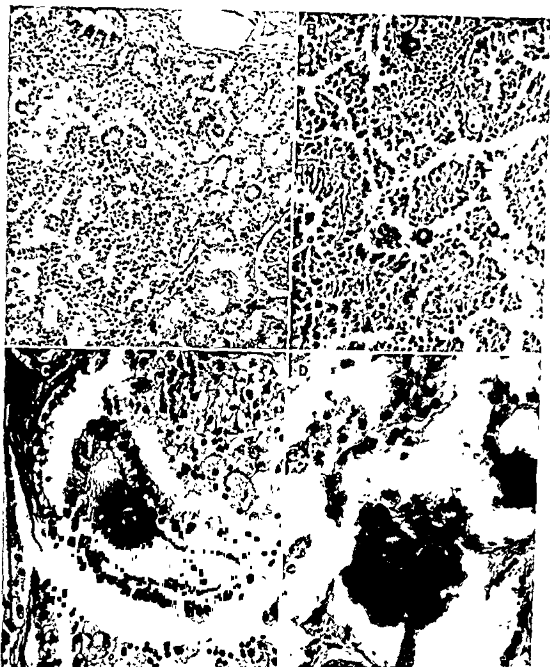



FIG A *Nonencapsulated tubular papillary cystadenoma*, showing origin from tubular epithelium in multiple foci

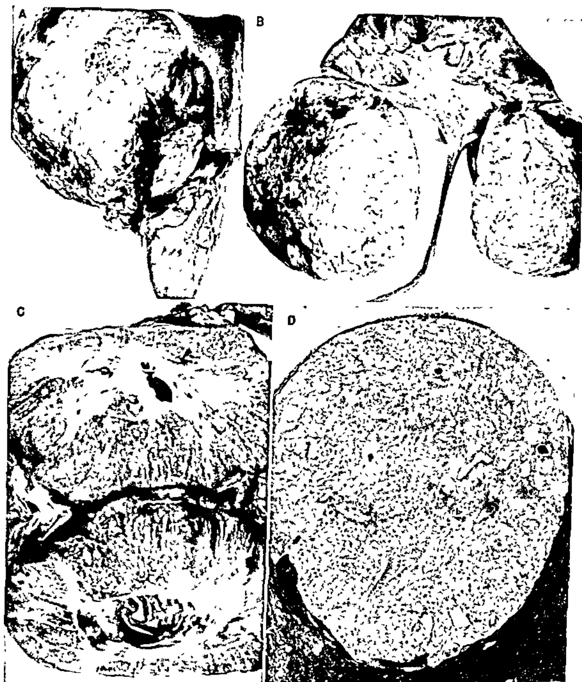
FIG C *Calcified body* within serum of venule of *frond of a tubular adenoma.*

FIG B *Psammomatous bodies* in the fronds of a papillary adenoma

FIG D *Calcific body* resulting from encrusting of epithelial cells of a papillary adenoma




FIG A *Partially trabeculated cyst* of upper pole of kidney with small papillary adenoma illustrated in figures B and C




FIGS A AND B *Circumscribed solid tubular adenoma* of kidney and dilated pelvis (B) resulting from pressure by the tumor (J Urol *56* 719–721, 1948)

FIG C *Circumscribed cortical (tubular) adenoma* of kidney with central cyst

FIG D *Cortical (tubular) adenoma* (1 5 cm in diameter) with compression of adjacent parenchyma into a pseudocapsule Unlike those in figures A, B, and C, this one would most probably have eventually metastasized




Fig A *Cortical (tubular) adenoma* sharply delimited from adjacent renal parenchyma

Fig B *Papillary cortical (tubular)* adenoma

Fig C *Cortical (tubular) adenoma* of kidney The individual cells resemble those of distal convoluted tubules

Fig D *Cortical (tubular) adenoma* of kidney with ossification of adjacent lipoma of cortex

despite a report of abnormal cytology in the urinary sediment.

*Experimental renal carcinogenesis*

Experimentally, cortical adenomas and low-grade adenocarcinomas have been produced bilaterally in the kidneys of male hamsters in which pellets of diethylstilbesterol were implanted subcutaneously. No tumors were induced in females, nor in those males in which the pellets contained cholesterol in addition to diethylstilbesterol (Kirkman and Bacon).

*Classification*

Again, as with most classifications in pathology, the overlapping of origins, cellular patterns, and the differences of opinion with regard to their nature and significance, leave any categorization of renal tumors open to some criticism. The outline used here has no real advantage over others, but it does include the division of hamartomas which serves a purpose if it is only to give opportunity to define and illustrate a much confused term. The other major source of difficulty in attaching a name to renal neoplasms, especially the carcinomas, is the diversity and prognostic meaning of their various cellular types.

### Classification of Renal Tumors

*Tumors of the Renal Parenchyma*

Benign
- Cortical (tubular) adenoma
  - Solid
  - Cystic
- Fibroma
- Lipoma
- Myxoma
- Angioma
- Lymphangioma
- Hemangiopericytoma
- Leiomyoma
- Mixed tumor with combination of above elements: angiomyolipoma, myxolipoma, etc
- Dysontogenetic rests
  - Adrenal cortical rests
  - Chondral and osseous rests
  - Dermoid cysts
  - Endometrioma

Malignant
- Adenocarcinoma (tubular) (Grawitz tumor; hypernephroma)
- Wilms' tumor
- Fibrosarcoma
- Liposarcoma
- Leiomyosarcoma
- Angiosarcoma and other compounded sarcomas
- Metastatic tumors

*Tumors of the Renal Pelvis*

- Papilloma
- Papillary transitional cell (epidermoid) or squamous cell carcinoma
- Nonpapillary transitional cell (epidermoid) or squamous cell carcinoma
- Mucous adenocarcinoma

*Tumors of the Renal Capsule*

- Fibroma
- Lipoma
- Angioma
- Leiomyoma
- Myxoma
- Tumors with combinations of the above elements and their malignant counterpart

*Tumors of the Paranephric Tissue*

- Tumors of type found in renal capsule
- Extra-osseous osteogenic sarcoma

## Tumors of the Renal Parenchyma

### *Cortical (Tubular) Adenomas*

Cortical (tubular) adenomas are a common incidental finding at postmortem examinations of people past middle age, occurring in about 4 per cent of kidneys examined at autopsy. They are usually pinhead sized to about 3 cm. in diameter (plate 271A), but may become huge

Fig A *Adrenal gland* growing both within the renal parenchyma and extracapsularly. Histologic section is shown in figure D

Fig B *Adrenal cortical rest* (arrow) is grossly similar to a cortical lipoma or adenoma

Fig C *Adrenal cortical rest.* The adrenal cells are in the upper two-thirds of the photomicrograph, renal tubules are in the lower portion.




(Legends on facing page)



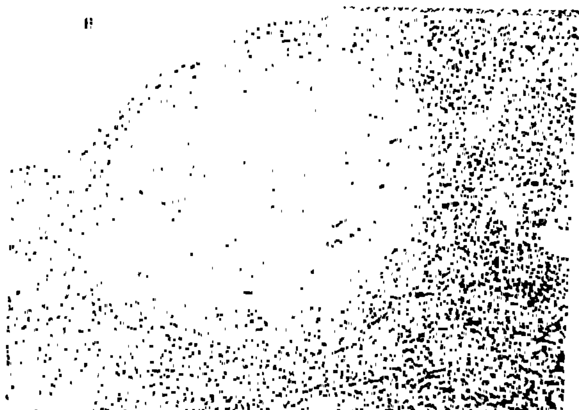



FIG A *Medullary fibromas* (arrows)

FIG B. *Medullary fibroma* with a few isolated residual tubules that are commonly found in these lesions




FIG A *Medullary fibroma* with tubular inclusions and the characteristically loose stroma which is often partially hyalinized

FIG B *Cortical fibroma* of identical pattern as the medullary fibromas These cortical fibromas are much less common

FIG C *Mild lipomatosis* secondary to parenchymal atrophy In extreme forms, the fat may occupy the whole original volume of the kidney and the perirenal fat may also be markedly increased

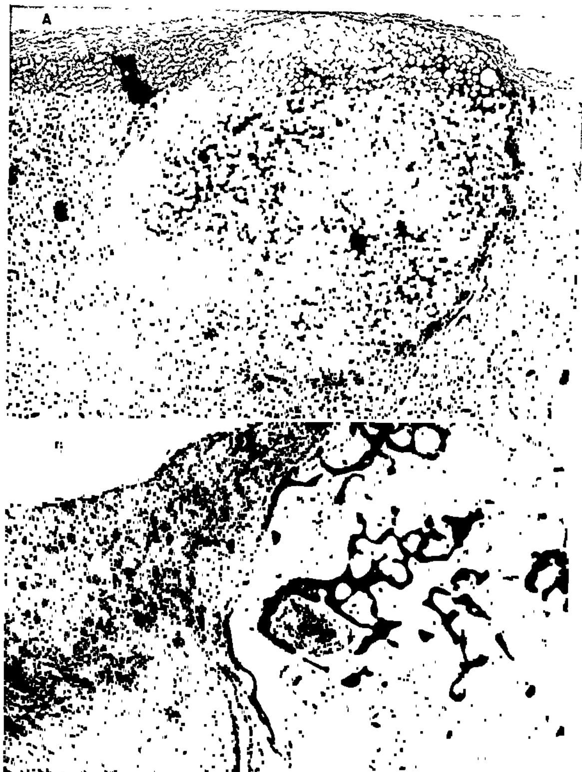


FIG A *Cortical lipoma of kidney*

FIG B *Cortical osteolipoma of kidney* The bone is a result of metaplasia rather than dysontogenesis







FIG A. *Hemangioma of kidney* (arrows) with blood clot in adjacent calyx and pelvis

FIG B *Hemangioma of kidney,* this photomicrograph is taken from lesion in figure A Such lesions may cause massive or fatal hematuria

FIG C *Varix of the kidney* This lesion is commonly mistaken for hemangioma or lymphangioma of the kidney

and develop into a mass about the size of a grapefruit (plate 274A, B, C) They may be cystic or solid The cystic ones often develop in cortical scars and are somewhat reminiscent of the papillary hydrocystadenomas of sweat gland origin that seem to follow occlusion of the duct of the sweat gland in some cases. Bell is confident that the renal papillary cystadenomas *do not ever become metastasizing carcinomas*; others disagree (Cristol et al , Cabot and Middleton, Leary) Papillary cystadenocarcinomas do occur

The solid ones are yellow, soft, spherical nodules located often immediately subcapsular, but also in other portions of the cortex The smaller tumors may be grossly indistinguishable from adrenal cortical rests, lipomas, angiomyolipomas, leiomyomas and the cortical fibromas. Cortical (tubular) adenomas rarely cause symptoms, although the larger ones (plate 274A, B, C), of which 50 were in the literature up to 1950 (*Cristol et al*), may result in hematuria, hydronephrosis, pain, and a palpable mass. The large clinically evident adenomas occur equally in both sexes (Cristol et al ), although the small incidental ones are about three times as common in men (Cristol et al ) Bell states that he arbitrarily classifies all "solid adenomas" larger than 3 cm in diameter *as carcinoma* Obviously there are many exceptions to this rule

*Histologic appearance*

The early, or better, smaller tubular adenomas—particularly those that consist of small cysts with proliferation of only a small portion of the lining—clearly indicate their origin from *tubular epithelium* rather than adrenal cortical rests It is this stage of the tubular adenoma which has led to the almost general replacement of the old concept that the Grawitz tumor is derived from adrenal rests within the kidney (hence, the old term "hypernephroma") by the concept of their derivation from renal tubular epithelium or renal tubular adenomas (Cristol et al ) In the very small cysts, the residual tubular epithelium, not yet converted to adenoma, appears indistinguishable from that of distal convoluted tubules, and *occasionally* from the proximal convoluted tubules (plate 271B, C). Cholesterol and birefringent crystalline cholesterol esters, and occasionally glycogen may be present in the cells; often lipid histiocytes are prominent in the interstitium. The neoplastic cells are usually remarkably uniform in size and shape, and *mitotic figures or evidence of* anaplasia is most uncommon. In some of the larger tumors, the vascularity is conspicuous, often in the form of dilated thin-walled sinuses.

In the cystic tumors, a nidus of papillary proliferation begins often at one segment of the epithelial lining and may or may not progress to obliterate the cavity. The papillary fronds *may become markedly edematous (plate 273)*

*Adrenal Rests*

Small, single or occasionally multiple, tawny soft nodules of adrenal cortical tissue, averaging 3–5 mm. in diameter, are found in the subcapsular regions of the kidney (plate 276B), usually near the superior pole, in about 1 per *cent of routine autopsy material. Obviously*, the disparity in reported incidence of such rests reflects the care of the observers in their search for these small bodies Histologically the nodules are composed only of adrenal *cortical* tissue (plate 276C), of course, and all three zones may be present although the reticularis is noted less often than the glomerulosa and fasciculata. *These rests have no apparent clinical significance.* There is no longer any but the most tenuous evidence to support the concept that the rests give rise to "hypernephromas" (clear cell renal adenocarcinoma). The association of the adrenal rests with papillary cysts or with renal carcinoma in another part of the kidney can hardly be regarded as indicative of a histogenetic relationship, as some believe The coincidental finding of renal clear cell adenocarcinoma and adrenal rests in the same kidney is *therefore not unexpected on the basis merely* of chance occurrence.

In addition to rests of adrenal cortical tissue within the renal parenchyma, small *histologic* foci or nodules and plaques of bone and cartilage are occasionally found, particularly in the medulla The bone generally appears to be metaplastic rather than dysplastic rests The chondral foci are usually true rests composed of hyaline cartilage and are said never to be found

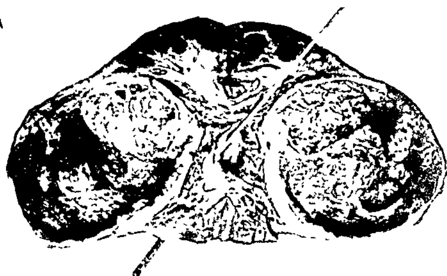


FIG A *Endometriosis of kidney* The hemorrhagic cyst occupies more than half of the kidney (Courtesy of Dr V E Marshall, J Urol *50* 652–656, 1943)

FIG B *Endometriosis of kidney* This photomicrograph was taken from a section of lesion illustrated above, and shows easily recognizable endometrial glands and stroma Only two such cases have been reported

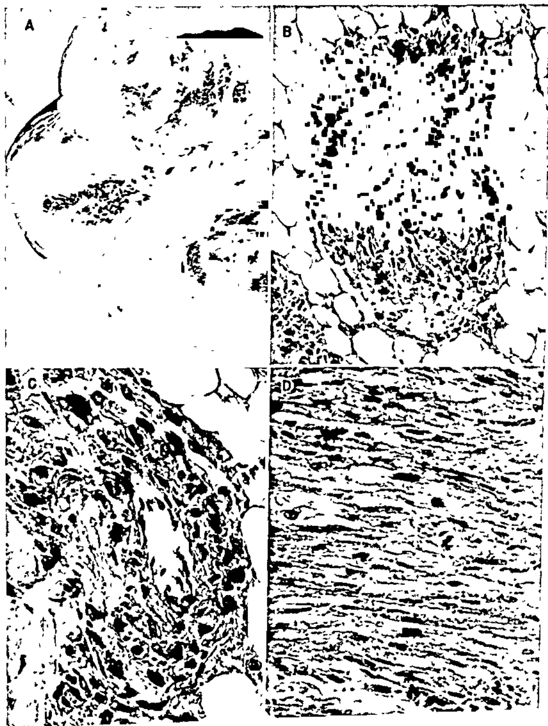



FIG A *Angiomyolipoma of kidney* Soft, unencapsulated, yellowish-red mass projecting from the cortex.

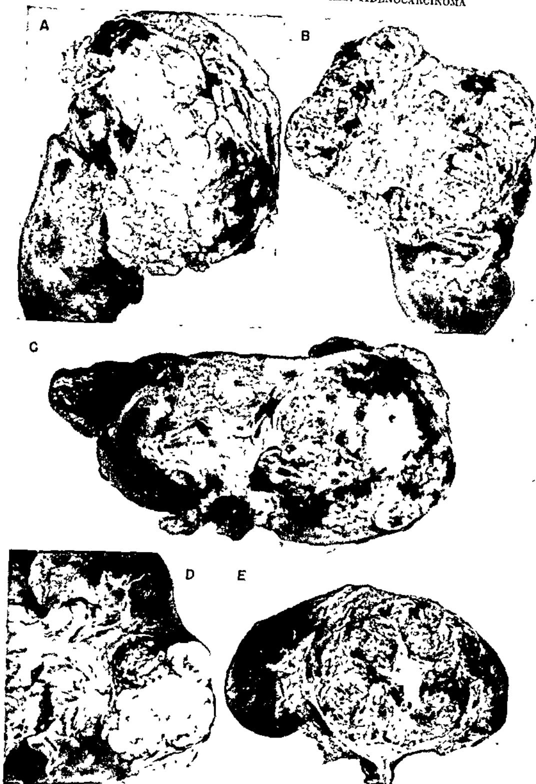
FIG B *Angiomyolipoma of kidney* with tumor cells radiating from the media of the vessels into the fat

FIG C *Angiomyolipoma of kidney* The tumor cells are clearly arising in the media of the vessel

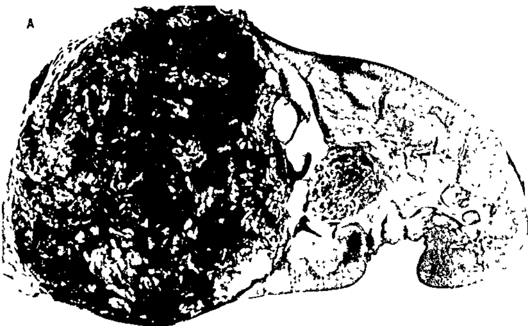
FIG. D. *Angiomyolipoma of kidney* showing purely myomatous variation in one portion




FIGS A AND B *Angiomyolipoma of kidney* showing the usual components of partially hyalinized vessels, fat and peritheliallly arranged muscle cells




FIGS A THROUGH E represent examples of *adenocarcinomas* (tubular) of the kidney, formerly called hypernephromas or Grawitz tumors



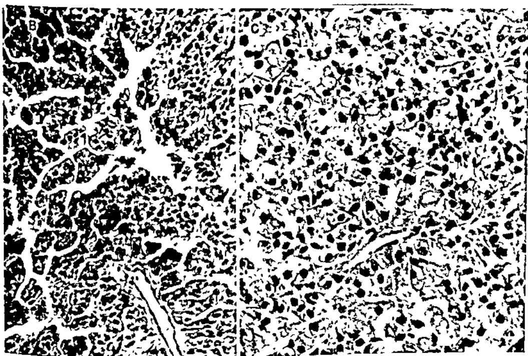




FIG A *Hemorrhagic papillary tubular adenocarcinoma* of upper pole of kidney with nodule of tumor in vein

FIGS B AND C *Papillary tubular adenocarcinoma* from tumor illustrated in figure A The cells have a granular cytoplasm

in kidneys without other congenital deformities (Killingsworth). However, although cartilaginous rests are commonly observed in association with cystic kidneys (plate 40B), they may be found also in neoplasms (plate 299B, C) and even in the absence of congenital anomalies of the kidney (plate 300A).

*Lipomas*

Lipomas are a fairly common tumor not only of the parenchyma but of the renal capsule and paranephric tissue The parenchymal lipomas are usually small spherical soft nodules of the order of 3 to 5 mm in diameter, located, as a rule, in the subcapsular portion of the cortex (plate 279A) Infrequently the lipomas from any of these sites of origin, but particularly from the paranephric fat, may become large and cause symptoms of any renal tumefaction (Robertson and Hand) A lipoma originating from the adipose tissue near the hilum may invaginate the renal pelvis and simulate a tumor arising from the pelvis

The lipomas are frequently compounded with hemangiomatous and myogenous components (plates 282B, C and 283A, B) to form tumors called angiomyolipomas or, more generally, hamartomas The affinity for hemangiomatous expansion in adipose tissue is well known in other locations, especially in the extremities. The muscle cells in these tumors have a peritheliomatous pattern and appear to arise from the media of the blood vessels (plate 282C) The proportion of fat, muscle and blood vessels is highly variable (plates 282, 283) Metastases from these lesions are an extremely rare occurrence Nevertheless, neoplasms that histologically merit the designation of liposarcoma occasionally occur (McCartney and Wynne) and instances of metaplastic ossification, of chondrification, of inclusions of striated muscle and even osteosarcoma have been described within pararenal lipomas (plate 279B), as in lipomas elsewhere (Binkley and Stewart)

The large pararenal lipomas cause symptoms in relation to the degree of compression of adjacent viscera, blood vessels and ureters (Gordon-Taylor). These tumors occur predominantly in males. The operative mortality on these large tumors is high (Pfeiffer and Gaudin) and the tendency for recurrence with increasing anaplasia is considerable. It is of interest that the pararenal lipomas do not diminish in size with cachexia of the patient (Pfeiffer and Gaudin)

*Liposarcomas*

Up to 1949, only 13 cases of liposarcomas of the renal parenchyma had been reported, according to Newman and Reed. Of these, 7 were associated with tuberous sclerosis Most of the tumors are large, and only histologically malignant; metastasis from these neoplasms has not been reported (Bell) The histologic picture is variegated (plate 317B C). Portions resemble a simple lipoma composed of adult fat cells, other parts contain embryonic, finely vacuolated fat cells, and still others take on the appearance of edematous, fibromatous or myxomatous tissue with abortive or typical Touton giant cells, and a basophilic mucoid matrix Isolated fibroblastic appearing cells have large, hyperchromatic irregular nuclei of sarcomas. Because the sarcomatous portions may be found surrounded by simple adult fat cells, the impression has been gained that liposarcomas may represent a malignant degeneration of a lipoma. If this is in fact what occurs, then the phenomenon constitutes additional evidence for an important oncologic principle, namely, that a benign mesenchymal tumor may undergo sarcomatous transformation, in contradistinction to its having been a sarcoma from its initial stages

*Lipomatosis*

True lipomas are to be distinguished from the progressive pelvic, peripelvic, and pararenal replacement accumulation of fat, or lipomatosis, in cases that show parenchymal renal atrophy (plate 278C) The over-all dimensions of the kidneys in these cases may be considerably enlarged by the pelvic and pericalyceal fat In one of Bell's cases, the kidney weighed over a thousand grams Calculi and pyelonephritis, or simple senile arteriosclerotic atrophy, are commonly associated with renal lipomatosis Renal lipomatosis may also be found in obese patients

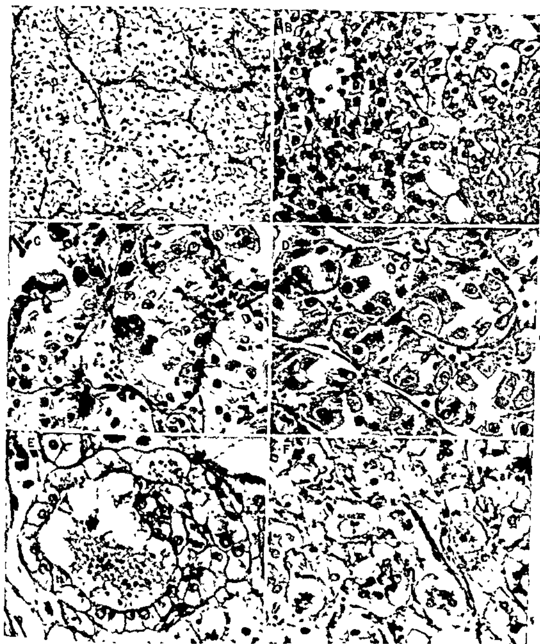



FIG A *Clear cell tubular adenocarcinoma*

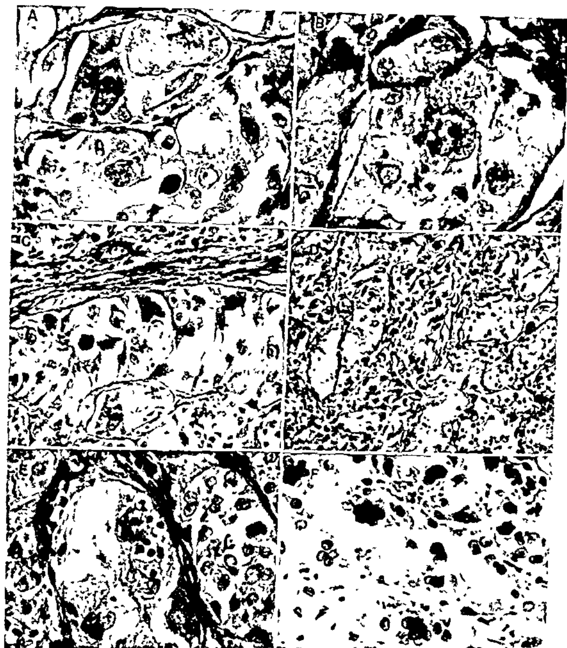
FIG B *Tubular adenocarcinoma* with granular and clear cells

FIG C *Tubular adenocarcinoma* with clear cells showing various degrees of granularity

FIG D *Tubular adenocarcinoma* composed of granular cells

FIGS E AND F *Tubular (clear cell) carcinoma* in which hemosiderin granules are noted within the cytoplasm, very much as in functioning tubules

# PLATE 287. MALIGNANT NEOPLASMS: TUBULAR ADENOCARCINOMA (HISTOLOGIC VARIANTS)




FIGS A AND B *Tubular adenocarcinoma* with huge, irregularly shaped nuclei and bizarre mitotic figures rather than the more usual uniform nuclei

FIG C *Tubular adenocarcinoma* with marked pleomorphism

FIG E *Polymorphonuclear leukocytes* are within the cytoplasm of a clear cell of a tubular adenocarcinoma as if they were phagocytosed by the cancer cell

FIG D *Tubular adenocarcinoma* with degrees of anaplasia varying in different fields

FIG F *Syncytium of nuclei* in a tubular adenocarcinoma simulating the syncytium that occurs normally in the proximal tubules in later decades

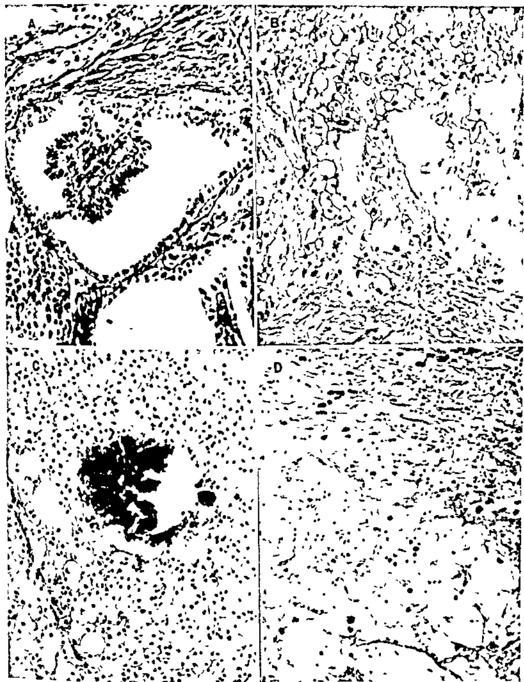
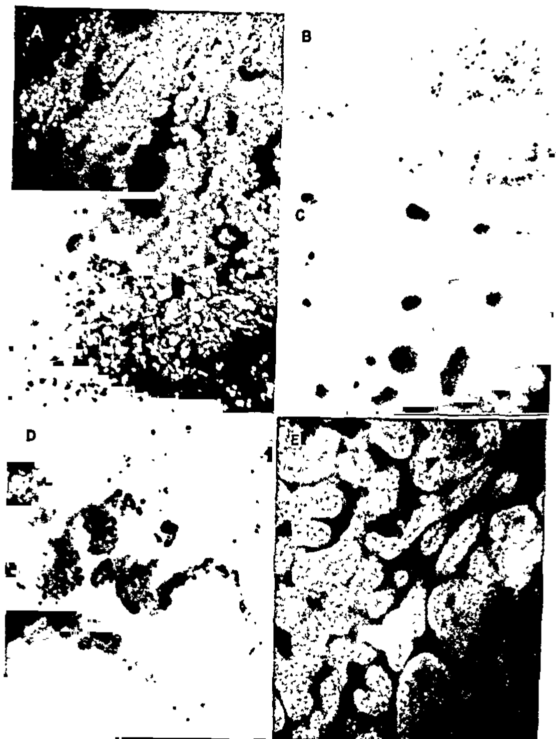



FIG A *Papillary cystadenocarcinomatous variant* of renal adenocarcinoma

FIG B *Glycogenic and lipid vacuolization* in renal adenocarcinoma

FIG C *Focal calcification* in renal adenocarcinoma, occasionally visible in roentgenograms

FIG D *Hemosiderin* in renal adenocarcinoma following spontaneous hemorrhages




FIGS A THROUGH D represent the *fluorescence attributable to vitamin A* and shown here in renal adenocarcinoma FIGURE E shows the fluorescence in a cortical adenoma of the adrenal for purposes of comparison (Courtesy of Dr Hans Popper, *Arch Path. 32 258–271, 1941*)




FIG A *Variation in pattern* in adjacent fields in a renal adenocarcinoma

FIG B *Well differentiated* adenocarcinoma simulating distal tubules

FIG C. *Renal adenocarcinoma* with solid nests of uniform cells

FIG D *Renal adenocarcinoma* with interstitial foam cells.

*Fibromas*

Fibromas are not uncommonly found as greyish-white, spherical, single nodules, usually 3 to 5 mm. in diameter As a rule, they are located in the medulla (plate 277A, B), and much less frequently in the cortex or capsule They have clinical significance only rarely when they reach large size The fibroma described by Gordon-Taylor weighed 22 pounds.

Histologically small fibromas are characterized by the inclusion of isolated renal tubules (plate 278A) Even the massive tumor just referred to had such inclusions and led to the diagnosis of adenofibroma This tumor was intrarenal in location The tubules are absent, of course, in the capsular and paranephric fibromas. The impression is gained that the tubules do not represent part of the neoplastic process but rather are simply incidental inclusions. The term "myxofibroma" is often used gratuitously for fibromas that have become edematous

*Hemangiomas*

Hemangiomas of the kidney are relatively rare benign tumors which occur at any age, are usually single, and are situated in the medulla or pelvis, rarely in the cortex. The tumors vary from 1 to 2 mm to several centimeters in diameter, are spongy and dark red (plate 280A) Microscopically, they are found to be composed of thin-walled sinuses that often simulate lymphatic vessels, or sometimes, tubules (280B) The presence of blood in the lumens is diagnostically helpful, but, of course, blood may be found within lymphatic vessels or tubules Even the small hemangiomas may be responsible for sudden massive hematuria The hematuria may be irregularly intermittent, and associated with pain in the groin or flank The diagnosis can rarely be made preoperatively because of the small size of the lesions, and commonly the cause of the lesion is labeled "essential hematuria" The lesions may be difficult to demonstrate even in the actual specimen (Dorman and Fowler).

*Endometrioma*

According to Marshall, his is the only case of endometrioma of the kidney to have been recorded.* The tumor in this instance was not on the surface of the kidney but definitely intrarenal (plate 281A) We had the opportunity to examine this remarkable specimen grossly The tumor occupied the central portion of the 800 Gm. kidney, between its poles, and measured 10 x 13 cm It was an irregularly multiloculated cystic mass, containing about 500 cc. of blood and had solid, fleshy portions. The patient was a 40 year old Greek woman who had noted a tender mass in the left flank and had hematuria on one occasion The intravenous and retrograde pyelograms revealed marked calyceal deformity The function of this kidney was reduced There is little to be gained from our contributing to the controversy of the theories of dysontogenesis of an endometrial tumor in the kidney. The histologic features are definitely endometrial (plate 281B).

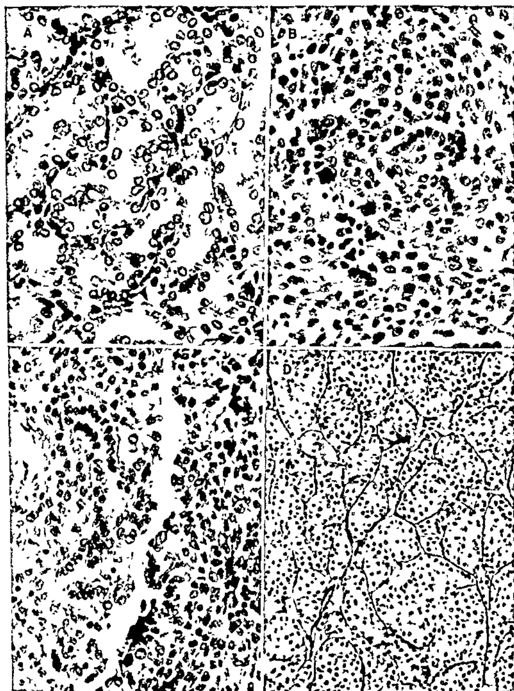
*Leiomyomas*

Small 3–5 mm leiomyomas are about as common as, and appear grossly similar to, the small fibromas, adenomas and lipomas. They are generally capsular or subcapsular. Occasionally, large parenchymal tumors are observed which seem to be composed entirely of fascicles of smooth muscle; others on careful search, are found to be predominantly leiomyomatous, but with foci of other elements, including clear cell carcinoma or areas suggesting renal blastema or Wilms' tumor The large leiomyomas often have features that warrant the histologic diagnosis of leiomyosarcoma and occasionally these metastasize (Gordon, Kimmelstiel and Cabell; Cooke)

*Tuberous Sclerosis*

Tuberous sclerosis is a familial disease of children and young adults characterized by progressive mental deterioration, epilepsy, sebaceous adenomas of the face and phacoma of the retinae. Nodosities of glial scars (tuberous sclerosis) are found in the cerebral cortex and, in over half the cases, there are associated hamartomas of various sorts in the kidneys. These renal tumors are usually multiple, of small size

* A second case of renal endometriosis has been reported recently. J Urol 64 566, 1950




FIGS A THROUGH D represent *variants of the well differentiated adenocarcinoma* of relatively good prognosis. The basis for evaluating the malignancy of this type of neoplasm is often arbitrary and dependent on its size.




FIG A *Cavernomatous sinusoids* in renal adenocarcinoma, thin walled and gaping for the reception of neoplastic cells

FIG C *Metastases to venules* of kidney from renal adenocarcinoma

FIG B *Metastases to intrarenal lymphatic vessels* from renal adenocarcinoma Such widespread lymphatic involvement has offered clues to the anatomy *of renal lymphatics*

FIG D *Isolated cells* from adenocarcinoma (clear cell) in renal vein, possibly artefactually included in view of their lack of cohesion.

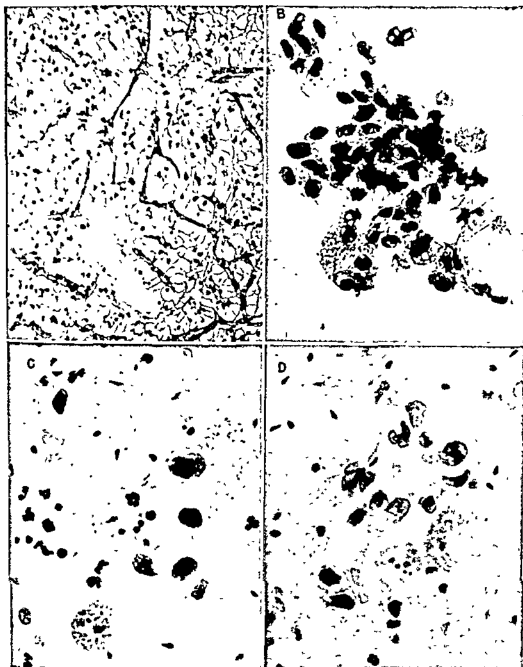



FIG A *Renal adenocarcinoma (clear cell)* which gave rise to cells in urinary sediment illustrated in figures, B, C and D

FIG B *Smear of urinary sediment* (routine hematoxylin-eosin stain) showing neoplastic cells of tubular adenocarcinoma in figure A

FIGS C AND D *Section of paraffin block of sediment of urine* from the patient with the adenocarcinoma of figure A showing neoplastic cells and, incidentally, spermatozoa



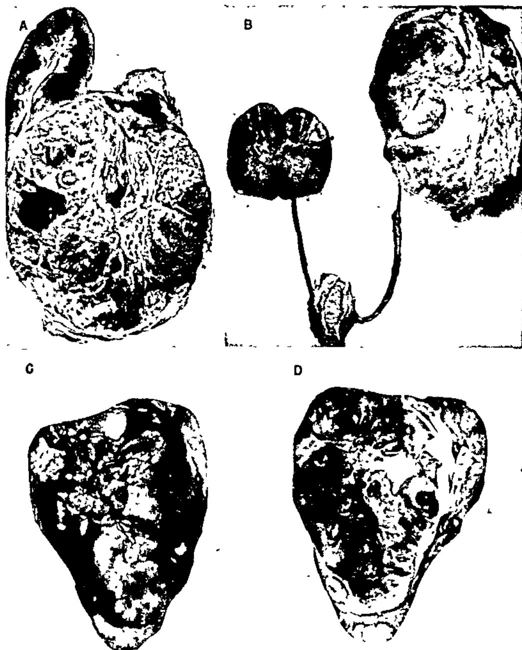

FIG A *Small adenocarcinoma* of the kidney which, despite its size, yielded enormously widespread metastases including some to the myocardium (figure E) The central portion of the tumor is of the clear cell variety, the rim is made up of highly anaplastic sarcomatoid cells The latter were responsible for most of the metastases The vertebrae pictured beside the kidney contain metastatic deposits

FIG B *Clear cell component* of the adenocarcinoma in figure A

FIG C *Aspiration smear* form a vertebra showing metastatic renal carcinoma from lesion of figure A

FIG D *Spindled carcinomatous component* from the periphery of the tumor in figure A

FIG E *Extensive metastases* to the heart from the small tumor in figure A




*Wilms' tumors of infants* showing cystic, trabecular, hemorrhagic and solid fleshy variations in structure, along with pseudocapsules

and consist of *lipomas, fibromas, angiomas,* leiomyomas, adenomas, as well as complex mixtures of the various elements of such growths (plates 282, 283) In some cases, the pyelograms of these kidneys may be mistaken for polycystic disease (Melicow) *Rarely sarcomatous change* occurs but metastases have not been recorded as far as we are aware Rarely, too, the tumors may be large and may thereby interfere with renal function In addition, rhabdomyomas of the myocardium or glycogen masses simulating rhabdomyomas, are found with tuberous sclerosis.

*Lindau's disease* consists of angiomas of the retina (or von Hippel's disease) and cerebellum, associated with syringomyelia, hydromyelia, cysts of the liver, pancreas and kidney, and angiomas, adenomas or carcinomas of the kidney (Davison et al.)

### *Parenchymal Sarcomas*

Exclusive of the Wilms' tumors which are often called adenosarcomas, sarcomas of the *renal parenchyma are rare* The reports would be even more scarce if sarcomatoid, spindle cell, anaplastic carcinomas, the lymphomas, and Wilms' tumors that masquerade as uniform spindle cell sarcomas in a given section, were properly pruned from these reports Moreover, some of the reported fibrosarcomas are, in reality, leiomyosarcomas, and liposarcomas may be erroneously labeled fibrosarcomas, fibromyxosarcomas or myxosarcomas, round cell sarcomas may actually be lymphomas, embryonal myosarcomas, or anaplastic carcinomas Occasionally Wilms' tumors of adults may present themselves as predominantly leiomyosarcomatous. In 1932, Judd and Donald reported 20 histologically documented cases of sarcoma (3 5 per cent) in a series of 570 renal cancers Eight others were suspected of being sarcomas, but histologic proof was lacking The tumors of children were excluded from these 28 cases The diagnoses included. fibrosarcoma (6), sarcoma, type undiagnosed (6), spindle cell sarcoma (3), round cell sarcoma, liposarcoma, myxosarcoma, fibromyxosarcoma, mixed-cell sarcoma, and fibrosarcoma-adenocarcinoma (1 each) Sarcomas of the adult kidney metastasize with great rarity although they may reach a huge size, and thereby add to the operative hazard.

## Renal Adenocarcinoma

### *Definition*

The term renal adenocarcinoma is used here instead of hypernephroma or Grawitz tumor. *It is now reasonably clear that this neoplasm,* with possibly rare exceptions, arises from the tubular epithelium, usually beginning as an "adenoma," rather than from adrenal rests residing within the parenchyma of the kidney. The qualifying *terms granular cell, clear cell,* spindle cell or heterocellular adenocarcinoma now often appear artificially and insignificantly distinctive, although perhaps some such differentiation may ultimately be paralleled with a biochemical or functional counterpart.

### *Incidence*

The parenchymal adenocarcinomas comprise 9 out of every 10 malignant tumors of the kidney and about 3 per cent of visceral cancers. These tumors occur predominantly in the sixth and seventh decades, and rarely before the age of 30 *For reasons altogether unclear, there is a* distinct preponderance of these tumors among males, a ratio of approximately 7 to 3 (Priestley) If the adenocarcinomas represent a degeneration of an adenoma, it would be expected that there *would be a corresponding predominance* of such adenomas in males. Actually the over-all incidence of the adenomas *is* more common in males (Leary, Cristol et al ). In Cris-

Fig A *Wilms' tumor* showing peripheral distribution *of the neoplastic tissue corresponding* to the peripheral distribution of the actively proliferating portion of the metanephrogenic renal blastema (figure C)

Fig B *Wilms' tumor* of figure A, illustrating the close resemblance of the neoplastic tissue to the renal blastema

Fig C *Embryonic kidney* of 3 cm fetus showing the similarity of the peripheral, multipotent cells to those of the Wilms' tumor.



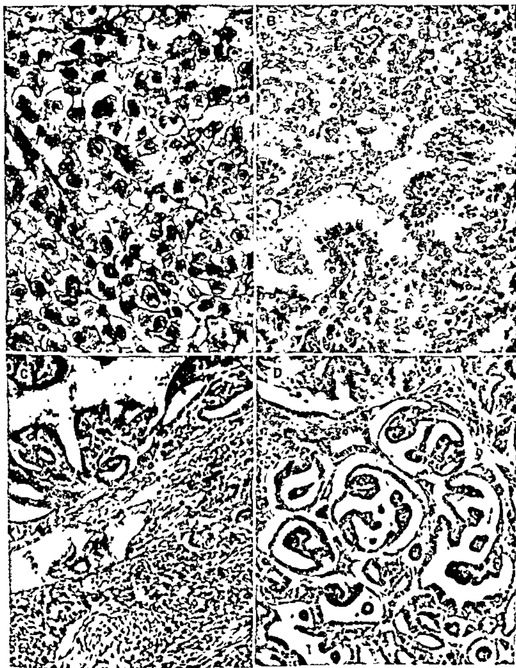

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## PLATE 297. Malignant Neoplasms: Wilms' Tumor




Figs A and B *Pseudoglomerular structures and calcific concretions* in a Wilms' tumor characterized by a prominent epithelial component There are many tubules, some partially invaginated simulate embryonic glomeruli, others of small size may be confused with rosettes Calcification may be sufficiently marked to be visible in a roentgenogram

Figs C and D *Pseudoglomerulus* in a Wilms' tumor In this instance, the pseudoglomerulus is the result of invagination of a neoplastic tubule by the peritubular sarcomatous element There is some similarity between the pattern of development of these pseudoglomeruli from the neoplastic tubules and the normal pattern of fetal development of glomeruli (plate 296C)




*Histologic variations in Wilms' tumors*

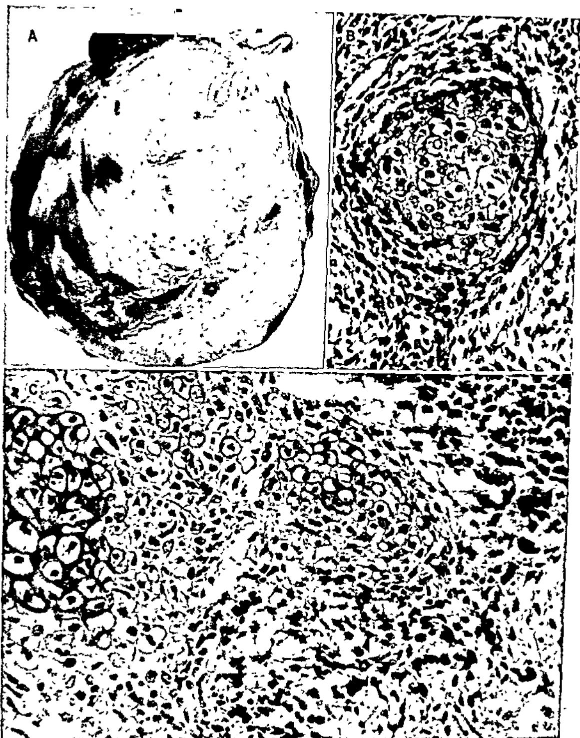



FIG A *Wilms' tumor* made up of solid, resilient, partially chondrified tissue

FIG B *Islet of cartilage* in a Wilms' tumor simulating squamous cell epithelium

FIG C *Intimate admixture of hyaline cartilage and other neoplastic elements in a Wilms' tumor* The hyaline cartilage appears to have been formed by metaplasia of neoplastic cells rather than as a result of dysontogenetic chondral rests of the sort illustrated in figure A, plate 300




FIG. A *Benign chondral rest* in the medulla of otherwise normal kidney of an infant

FIG. B *Pseudocapsule* at the periphery of a Wilms' tumor

FIG. C *Abortive tubular formation* in a Wilms' tumor. This pattern resembles the multipotent tissue present at the periphery of an embryonic kidney




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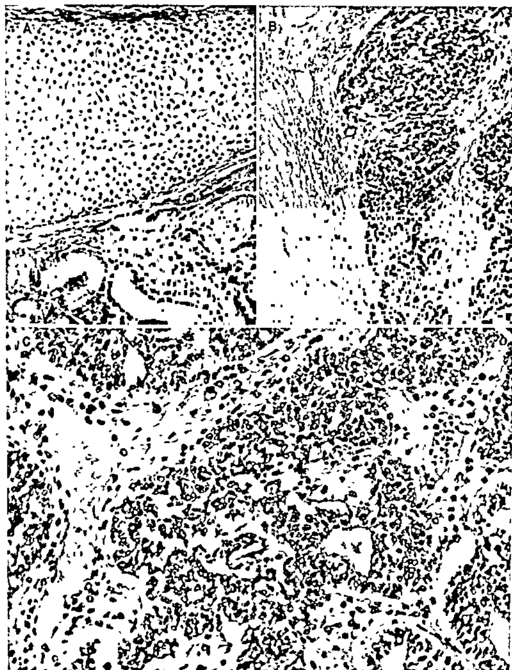



FIG A *Benign chondral rest* in the medulla of otherwise normal kidney of an infant

FIG B *Pseudocapsule* at the periphery of a Wilms' tumor

FIG C *Abortive tubular formation* in a Wilms' tumor This pattern resembles the multipotent tissue present at the periphery of an embryonic kidney

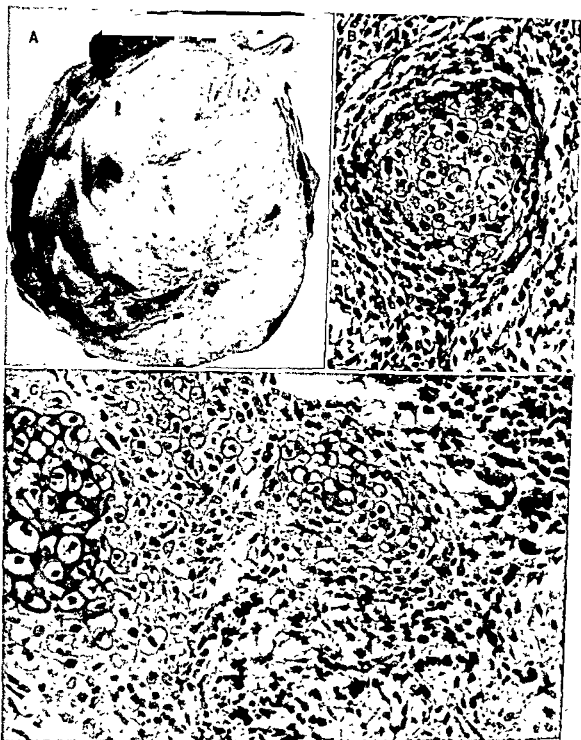



FIG A. *Wilms' tumor* made up of solid, resilient, partially chondrified tissue

FIG B *Islet of cartilage* in a Wilms' tumor simulating squamous cell epithelium

FIG C *Intimate admixture of hyaline cartilage and other neoplastic elements in a Wilms' tumor* The hyaline cartilage appears to have been formed by metaplasia of neoplastic cells rather than as a result of dysontogenetic chondral rests of the sort illustrated in figure A, plate 300

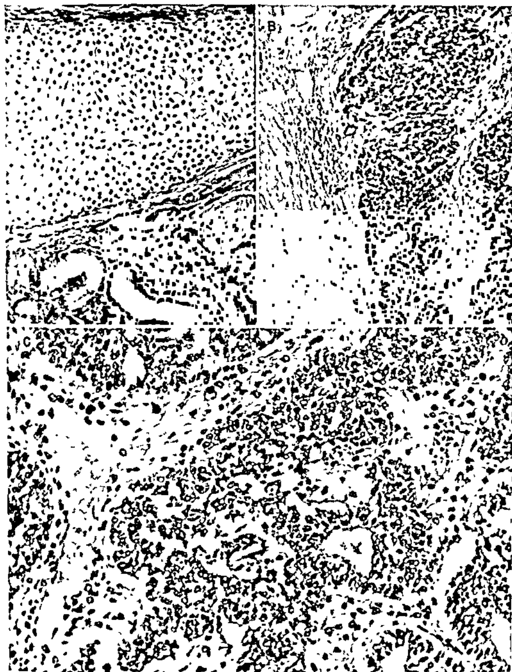



FIG A. *Benign chondral rest* in the medulla of otherwise normal kidney of an infant

FIG B *Pseudocapsule* at the periphery of a Wilms' tumor

FIG C *Abortive tubular formation* in a Wilms' tumor This pattern resembles the multipotent tissue present at the periphery of an embryonic kidney

tol's series, the incidence of adenomas was 5.8 per cent in males, as against 1.3 per cent in females.

In a remarkably high number of cases, the initial symptoms, unfortunately, are not caused by the direct mechanical or invasive effects of the primary tumor, but by its metastases to lungs and bones. Astonishing instances of regression of pulmonary metastases following the removal of the primary renal adenocarcinoma have been reported (Mann, Bumpus, Willis). There appears also to be adequate justification for removal of a single metastasis after the primary tumor is controlled even if it requires a pulmonary lobectomy, as the case of Barney and Churchill proves.

In Priestley's series of 502 adenocarcinomas, 47.7 per cent survived more than 3 years, 38.4 per cent more than 5 years and 27.3 per cent more than 10 years. This survival rate is much greater than that for the carcinomas of the renal pelvis, particularly the nonpapillary ones.

The renal carcinomas frequently metastasize to lungs (57 per cent), bones (32 per cent), regional lymph nodes (41 per cent), liver (27 per cent) and adrenals (11 per cent). From about 8 to 18 per cent of renal adenocarcinomas metastasize to the opposite kidney, a feature that must be evaluated carefully in the determination of independent bilateral origin of these tumors. Other organs to which metastases seed are brain, thyroid, heart, peritoneum, spleen, skin and ureter. Odd locations for metastases are also often selected, such as the tonsil, larynx and iris.

## *Pathology of Renal Adenocarcinoma*

### *Gross appearance*

The primary renal adenocarcinoma may come to occupy any portion of the parenchyma, the poles or the central portion, and varies in size from 3 cm. to huge dimensions. However, the small tumors arise almost exclusively in the cortex. The largest in Bell's series weighed 3300 Gm. The diameter of 3 cm. is arbitrarily selected by Bell as the borderline between the benign tubular adenoma and the adenocarcinoma because only one of 45 tumors less than 3 cm. proved malignant. Actually, tumors less than 5 to 6 cm. in diameter rarely yield metastases. At this size, however, it may be impossible to be certain from the gross or even the microscopic examination if the tumor is cancerous or benign. Obviously, such arbitrary criteria of malignancy serve merely as a presumptive, exceedingly rough guide and are no more reliable for individual cases than is the use of 2.5 cm. as a criterion for judgment of the malignancy of gastric ulcers.

Renal adenocarcinomas (plate 284) are spherical or bosselated and moderately soft. On section they are bright yellow, and, especially in the larger tumors, mottled with deep red hemorrhagic and necrotic areas, and grey areas of fibrosis. The smaller tumors appear deceptively encapsulated, the larger ones invade the adjacent parenchyma and pararenal tissues, and show a particular propensity for entering the renal vein and extending in continuity up the inferior vena cava to the right heart. Becau the tumor may invade the renal vein as a sol cast prior to distant metastasis, surgeons ma remove this tongue of tumor, even if it extenc into the inferior vena cava, occasionally wit gratifying results.

### *Histologic appearance of renal adenocarcinom*

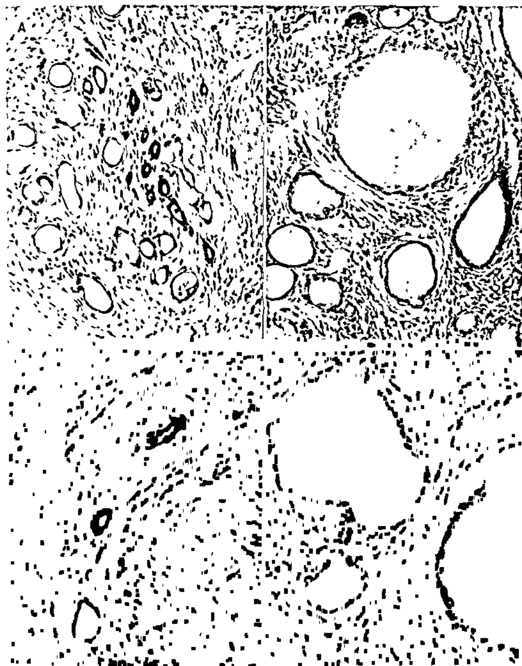
The histologic details are illustrated in plat 285 to 294. As with the adenomas, the cells fr quently resemble tubular epithelium closel Some of the tumors are made up entirely c clear cells with small uniform nuclei and cyt plasm containing lipid with vitamin A (Pop per) (plate 289), more or less glycogen, and un stainable hydropic vacuoles. The content c vitamin A is demonstrable with fluorescent mi croscopy. Other adenocarcinomas have clea cells mixed with granular cells (plates 285, 286 287), and still others have components of viru lent spindle cells (plate 294D) that are truly altered carcinomatous cells but may be mis taken for sarcoma or a variant of Wilms' tu mor. The granular cells are postulated by Melicow as being derived from the visceral o parietal glomerular epithelium or from granula cell adenomas. There is little to support this the ory of origin of these tumors from Bowman's epithelium. Occasional cells have inclusions o hyaline droplets, hemosiderin and lipochrom




FIG A *Well differentiated sarcomatous element* in Wilms' tumor with desmoplasia and focal fatty degeneration The field was representative of most of the tumor which nevertheless metastasized widely See figure B

in the primary neoplasm

FIG C *The epithelial and mesenchymal variation* in this portion of a Wilms' tumor is suggestive of the similar normal variations at the peripheral capsule of tissue of the embryonic kidney




Figs A and B *Microcystic and desmoplastic changes* after irradiation The dilated tubules represent viable tumor

Figs C and D *Spontaneous cystic change* in Wilms' tumor which might be mistaken for a polycystic kidney in a biopsy specimen

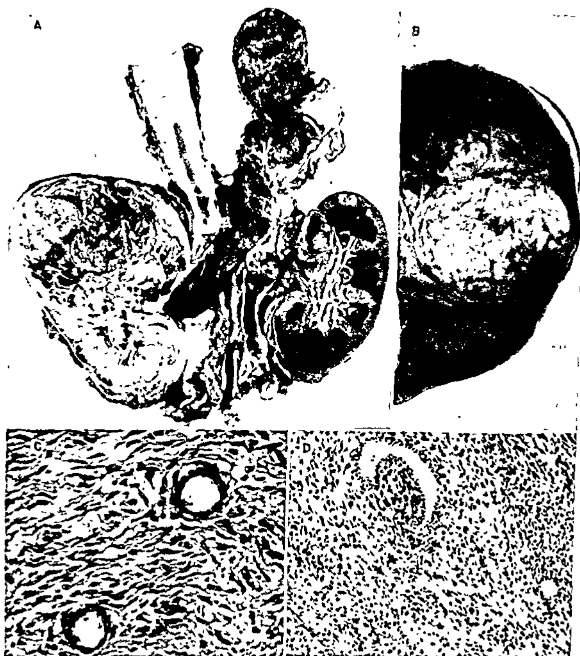



FIG A *Venous invasion* (*tumor thrombus*) from Wilms' tumor of the right kidney extending into renal vein and inferior vena cava Pulmonary metastases were present

FIG B *Small Wilms' tumor* discovered incidentally in the kidney of a 32 year old male who died from malignant nephrosclerosis (photomicrograph in figure D)

FIG C *Two tubules with single layered epithelium* caught in the sarcomatous element of Wilms' tumor

FIG D *Adenosarcomatous* features of Wilms' tumor of figure B




Fig A *Prominent muscle component* in a Wilms' tumor

Fig B *Cross striations* in muscle fibers in a Wilms' tumor (Masson trichrome stain)

Fig C *Muscle cells* in association with masses of neoplastic cells simulating lymphocytes in a Wilms' tumor

Fig D *Deceptively torpid and non-neoplastic appearance* in portion of a Wilms' tumor




FIG A *Carcinosarcoma of a kidney* composed of two fairly pure components (1) leiomyosarcoma and (2) clear cell carcinoma This case is from an adult

FIG B *Higher magnification* of the clear cell carcinomatous element in figure A The clear cell component may be so conspicuous as to lead to the erroneous diagnosis of a simple clear cell carcinoma or hypernephroma in children

FIG C *Myosarcoma of kidney* considered by many to be a variant of Wilms' tumor Muscle striations were present

FIG D *Large pure leiomyosarcoma* of kidney.

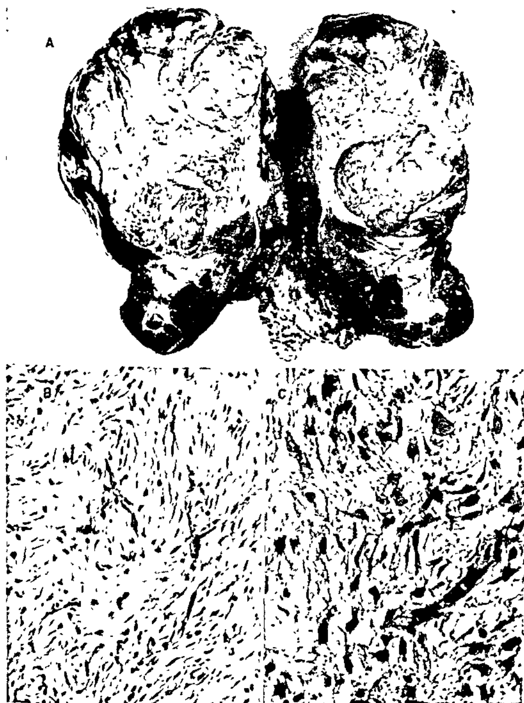



FIG A *Myosarcoma of the kidney* in a 32 year old patient resulting in death from massive local recurrence

FIGS B AND C *Loosely edematous myosarcoma of kidney* illustrated above Some observers regard renal parenchymal myosarcoma as a one-sided development of a Wilms' tumor

granules which suggest even a functional resemblance to renal tubular epithelium

The patterns are as variable as the cells and include solid, alveolar, papillary, tubular and cystic arrangement. Large, thin-walled sinuses ready to receive invading cells (plate 292A) are a characteristic feature of this tumor Foci of necrosis, calcification, desmoplasia, and old and recent hemorrhage vary the picture The spotty calcification may be visible in roentgenograms, and may be of diagnostic assistance, although it must be remembered that about 15 per cent of simple cysts show evidence of calcification (Cahill and Melicow). Attempts to gauge the prognostic significance of the different patterns and types of cells are not reliable, although the virulent sarcomatoid cells may be expected to metastasize early and extensively. The size of the tumor is the principal factor in prognosis, although, again, exceptions do occur (plate 294)

## Wilms' Tumor

### *Incidence, diagnosis and therapy*

Wilms' tumors constitute about 20 to 25 per cent of all malignant neoplasms of childhood, it is second in frequency to the neuroblastomas, according to Wells and most other observers The Wilms' tumors are practically the only malignant tumors of the kidney in this age group. Of 16,565 admissions for cancer to the Memorial Hospital, 0 1 per cent were for these tumors The majority of Wilms' tumors are observed before two years of age, about 90 per cent of them occur during the first seven years of life Undoubtedly some instances of reported "hypernephroma" in infancy represent variants of Wilms' tumor. It is stated that an analogous neoplasm is the commonest tumor of swine (Kretschmer and Hibbs), this latter neoplasm, however, rarely produces metastases. Any tumor of the abdomen in children should be considered to be a Wilms' tumor until proved otherwise Neuroblastoma of the adrenal, embryonal rhabdomyosarcoma, unilateral polycystic kidneys and unilateral hydronephrosis may simulate Wilms' tumor.

The visible and palpable mass may be the only symptom of the tumor and in most cases antedates pain and hematuria; the latter may not appear at all because of the failure of the tumor to communicate with the pelvis or tubules Wilms' tumors occur on either side with equal frequency and, unlike other malignant renal tumors, there is no sex predisposition The tumors grow rapidly, metastasize and cause death usually within a few months after discovery in most untreated cases. Metastases occur chiefly in the liver, lungs and regional lymph nodes, but may involve the brain, adrenals and other organs. The treatment of choice currently is nephrectomy supplemented with x-radiation. The matter of the use of x-radiation pre- and/or postoperatively, is handled differently in the various centers. The radiosensitivity varies markedly and apparently is dependent on the histologic structure of this highly variegated tumor (Kretschmer) Preoperative x-radiation certainly decreases the size of some of the tumors remarkably, thus facilitating the operative procedure

If recurrences are to take place, they generally do within the first two years after operation, although latent periods of ten years have been recorded. Five year cures are estimated at between 10 and 15 per cent (Hyman, Priestley and Schulte).

Although Wilms' tumors are principally tumors of childhood, they are not extremely rare in adults Sparks collected 26 cases in the literature up to 1942. Rarely, they are found incidentally at autopsy, as in the instance of the small one illustrated in plate 304B, which, although histologically malignant, had not yet metastasized This patient was a 32 year-old man who died of uremia with malignant hypertension The small size of the tumor and its out of the way cortical position suggested no relationship to the hypertension.

Fig A *Angiomyomatous polyps* at ureteropelvic junction These were ball-valve in action, blocking the ureteral catheter, but not the urinary outflow

Fig B *Section of angiomyomatous polyp* from figure A The whorls of muscle about the vessels resemble the pattern of the angiomyoma of the skin.

PLATE 308. Neoplasms of Renal Pelvis: Polypoid Angiomyoma




B

(Legends on facing page)

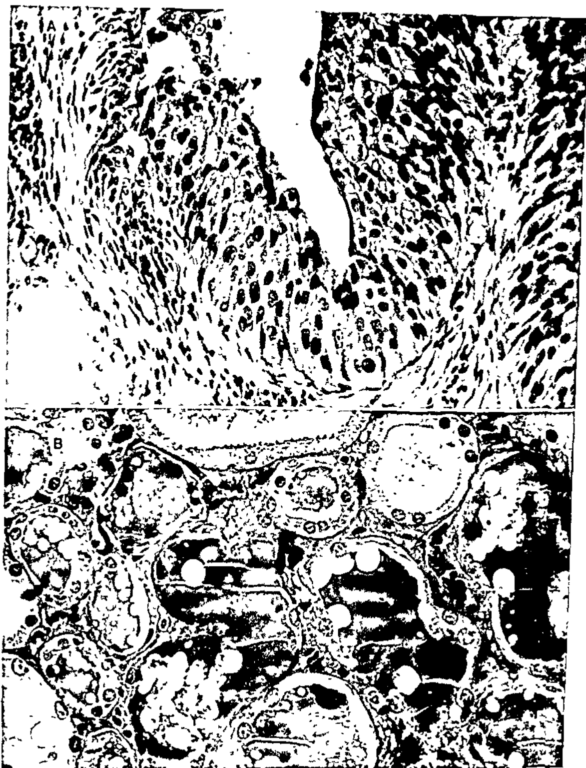



FIG A *Noninfiltrating epidermoid carcinoma* (carcinoma in situ) of pelvic epithelium

FIG B *Regenerating large hyperchromatic tubular cells*, from a case of acute glomerulonephritis, which could easily be confused with neoplastic cells in a smear of urinary sediment.

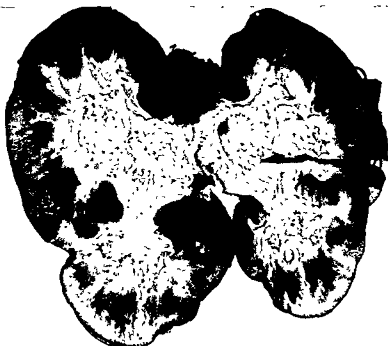





FIG A *Leukoplakia of pelvis and calyces* No calculi were present Section illustrated in figure B (A F I P Acc 17372)

FIG B *Keratinization of epidermalized calyceal mucosa* from kidney illustrated in figure A No dyskeratosis or anaplasia is included in this highly differentiated squamous epithelium The squamous metaplasia of the pelvic mucosa following infection or irritation by calculi, rarely produces this degree of keratinization and the cells are usually less differentiated However, leukoplakia of the renal pelvis, with or without squamous cell metaplasia, is prone to undergo carcinomatous transformation (compare plates 309A and 311A)

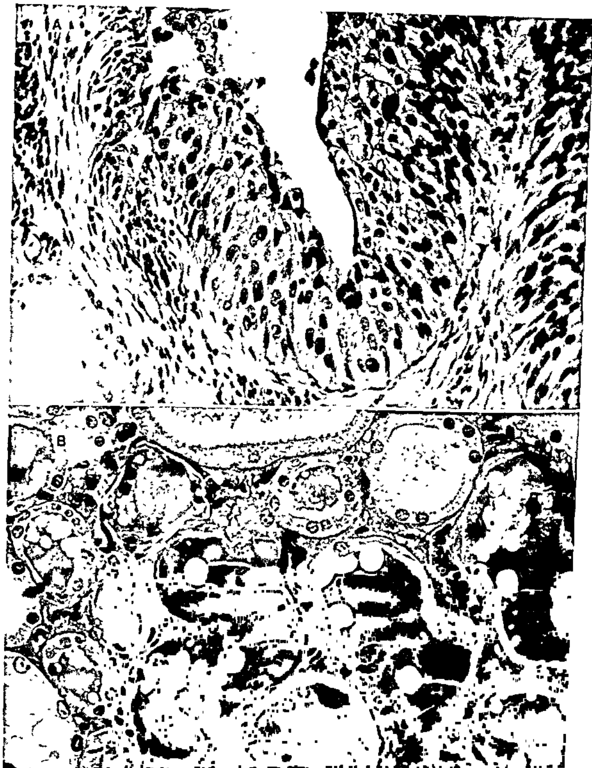



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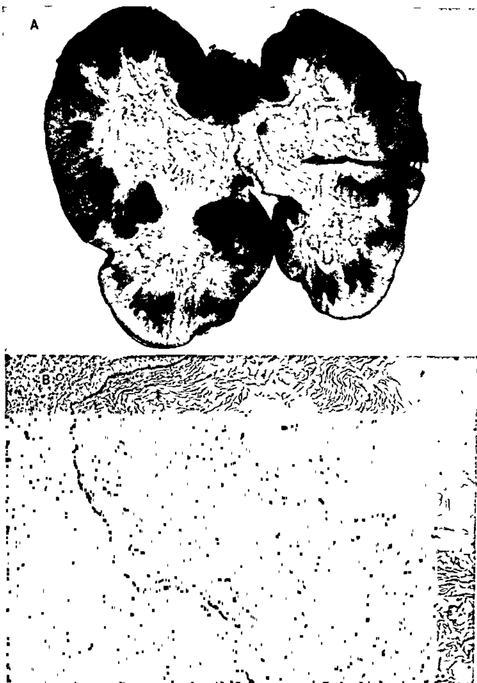



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FIG A. *Leukoplakia* of renal pelvis with epidermalization, from a case of calculous pyelonephritis

FIG B *Epidermoid carcinoma* from leukoplakic pelvis illustrated in figure A The carcinoma is so anaplastic that it might easily be mistaken for a metastasis or a variant of a Wilms' tumor

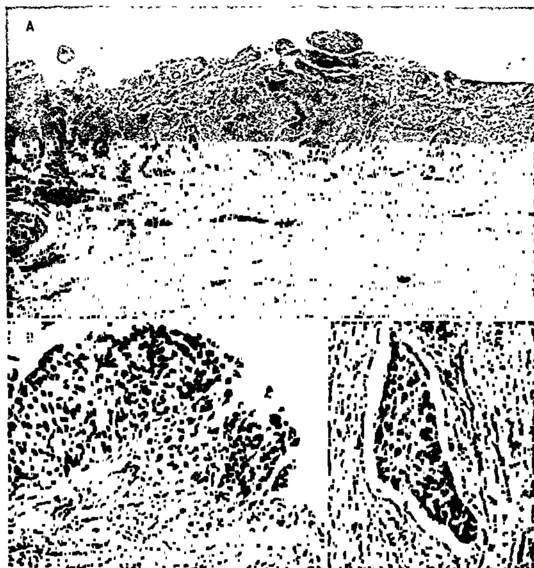



FIG A. *Papillary epidermoid carcinoma of renal pelvis* with extension to ureters and bladder A nest of tumor is present in a lymphatic vessel at the left

FIG B *Higher magnification of the papillary epidermoid carcinoma of figure A* The neoplasm in this field appears deceptively noninvasive

FIG C *Pelvic lymphatic invasion of the papillary epidermoid carcinoma illustrated in figures A and B*

## *Pathology of Wilms' Tumor*

### *Gross appearance*

The tumor may be situated in the center or at the poles of either kidney, or may replace the cortical area and rim the kidney (plates 295, 296A). Primary bilateral involvement rarely occurs. Small Wilms' tumors are rarely seen; the small one pictured in plate 304B is exceptional, as stated. The tumors generally are circular, expanding masses with a pseudocapsule. The tumors may reach huge proportions; several cases weighing 7 to 12 pounds have been reported and one weighing 30 pounds is described (Neff) They may compress the kidney markedly with resultant destruction of a considerable portion of the renal parenchyma.

The sectioned surfaces of the tumors are usually variegated so as to resemble ordinary teratomas, with irregular, solid and gelatinous, cystic and hemorrhagic areas (plate 295) Some, however, are as homogeneously fleshy as leiomyosarcomas (plate 299A)

### *Histologic appearance of Wilms' tumor*

The histologic variations in the Wilms' tumors are about as extensive as they are in teratomas of the testis. This feature is illustrated in plates 296 through 306 The element that has come to be recognized as the pivotal histologic feature of the Wilms' tumor is the abortive glomerulo-tubular structures with immature, hyperchromatic spindle cell stroma also known as "renal blastema" (plate 296B). These structures are more or less faithful modifications of glomerulo-tubular anlages that can be seen in the subcapsular portions of kidneys of young human embryos (plate 296C) These same structures are the essential reason for the use of "adenosarcoma" as a synonym for Wilms' tumor although often there are more overt sarcomatous components It might perhaps be added that the neoplasm labelled "glomeruloma" (Owen) has no relationship to Wilms' tumor The justification of this designation on the basis of the evidence thus far advanced is not convincing In Owen's case, the history of a previously resected carcinoma of the breast and the lack of an autopsy somewhat weaken the nosological position of the new term.

In addition to the haphazardly scattered proliferations of glomerulo-tubular structures, there are these other elements seen in Wilms' tumors: (1) foci indistinguishable from leiomyosarcoma, (2) foci of distinctly striated muscle which are present in a large percentage of Wilms' tumors (plate 305 B), (3) tubular cysts (plate 303), (4) fibromatous areas (plates 301A, 305D), (5) collections of small hyperchromatic cells that simulate neuroblastomas including rosettes (plates 297A, B; 333D), (6) chondral and osseous foci (plate 299), and (7) areas of degeneration including dense fibrosis, necrosis and lipid histiocytes (plates 301A, 302B)

*Metastases* may look entirely different from the primary tumor (plate 301A, B) This phenomenon is not unexpected in view of the kaleidoscopic composition of many of the primary tumors. As with other composite tumors, the most anaplastic element is likely to metastasize first and most abundantly There are exceptions to this rule, but it is clear that differences in radiosensitivity between the primary Wilms' tumor and its metastases are not unexpected. A *single* section of the primary tumor may reveal no area that resembles the metastases Another feature of the Wilms' tumor that merits emphasis is that fibrosis, deposition of lipid macrophages and necrosis may occur spontaneously and so simulate changes attributable to x-radiation (plate 302).

As indicated, the prognosis in cases of Wilms' tumor is grave It is hazardous to evaluate the prognosis on the basis of the histologic pattern of these neoplasms, especially if there is the temptation to be optimistic because of a relatively benign appearing cellular composition. The presence of venous invasion within the kidney is always an ominous sign.

## *Embryogenesis*

The Wilms' tumor has been responsible for an abundant, necessarily speculative literature dealing with the embryogenesis or possible anlage of the various components of the tumor. Individual theories have been constructed on the basis of preferential emphasis on the significance of the separate neoplastic elements or on the basis of inferences drawn from the association of two or more of such elements For

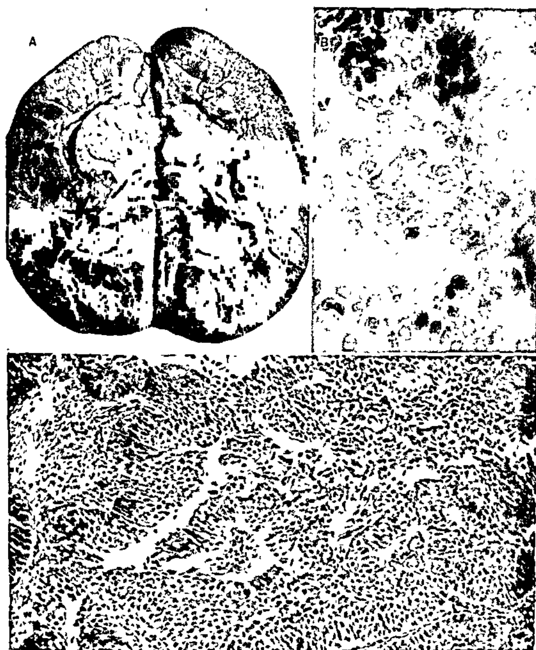
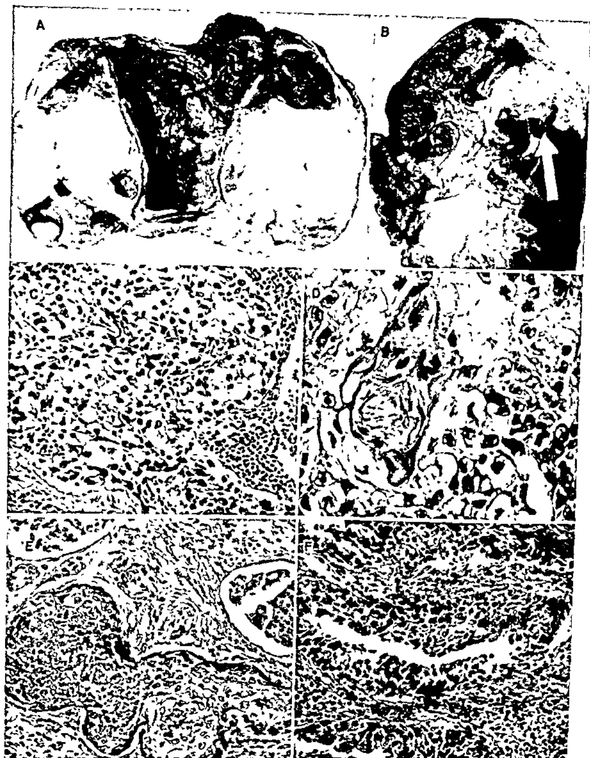



FIG A *Papillary epidermoid carcinoma of renal pelvis* This neoplasm has grown out into the pelvis and infiltrated only superficially in contrast to those in plates 311 and 314

FIG B *Smear of papillary epidermoid carcinoma* of figure A stained with hematoxylin-eosin A mitotic figure is included (arrow)

FIG C *Papillary epidermoid carcinoma* of figures A and B




FIGS. A AND B. *Virulent infiltrating nonpapillary epidermoid carcinoma* arising from calyceal epithelium.

FIGS. C AND D. *Infiltrating epidermoid carcinoma* arising from calyceal epithelium.

FIG. E. *Intrarenal lymphatic invasion* by epidermoid carcinoma of renal pelvis.

FIG. F. *Squamous metaplasia* in collecting tubules.




FIG A *Mucous adenocarcinoma of renal pelvis* (Histologic slide through courtesy of Dr A B Ragins)

FIG B *Mucous adenocarcinoma of renal pelvis* The histologic picture is indistinguishable from that of colonic mucosa (Histologic slide through courtesy of Dr L V Ackerman)







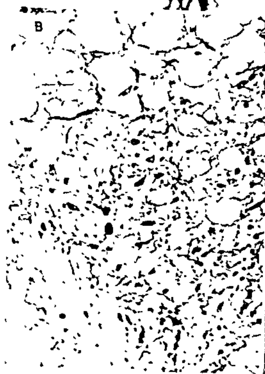



FIG A *Peripelvic lymphatic cysts* (Courtesy of Drs Joseph F Kuzma and W A D Anderson )

FIG B *Old hemorrhage into solitary cyst* of kidney The hemorrhage followed attempted aspiration of the cyst eight years previously

FIG C *Perirenal hematoma* from rupture of atherosclerotic aorta



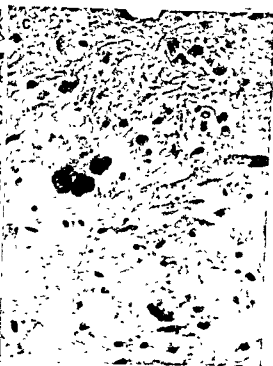




FIG A *Pararenal liposarcoma*, weighing approximately 1400 Gm

FIG B *Section from liposarcoma* of figure A, showing adult fat cells and hyperchromatic lipoblasts resembling fibroblasts

FIG C *Another field from liposarcoma* of figure A, in which an abortive Touton giant cell showing anaplasia is seen

example, the presence of striated muscle, smooth muscle, and cartilage has influenced thought in the direction of the origin of Wilms' tumors from the myotome The presence of actual and simulated nerve elements has won advocates to the neurogenous theory of the nature of many Wilms' tumors However, the concept that seems more often and more completely *in harmony with the histologic facts* attributes the genesis of the Wilms' tumor to the renal blastema, that is, to a neoplastic change in the renal anlage Because of the close simulation of the histological pattern of many Wilms' tumors to that of the nephrogenic cap (plate 296B, C) the impression of histogenetic relationship is easily achieved Moreover, occasionally a Wilms' tumor traverses the cortex much after the fashion of a nephrogenic cap (plate 296A)

The origin of the Wilms' tumor is not the same as that of the organoid teratoma Wilms' tumor clearly is of mesenchymal origin The *teratoma*, as it is generally defined, is a rare renal tumor derived from the three germ layers, endoderm, mesoderm and ectoderm, and *may include such structures as brain and intestines* (Lubarsch)

### Tumors of the Renal Pelvis

It is estimated that about 5 to 10 per cent of clinically apparent renal tumors are of the renal pelvis, and that malignant tumors of the renal pelvis are found in about 0 5 per cent of autopsies (Bell) These are divided approximately as follows:

| | |
|---|---|
| Papilloma | 30% |
| Papillary transitional cell, epidermoid or squamous cell carcinoma | 45% |
| Nonpapillary transitional cell, epidermoid or squamous cell carcinoma | 25% |
| Mucous adenocarcinoma | rare |

The majority of cases occurs between 40 and 60 years of age, although cases in infancy have been reported The predominance in the male of renal pelvic neoplasms, both papillary and nonpapillary, is somewhat greater than for the parenchymal tumors and is of the order of 2:1 to 3.1. The outstanding symptom is hematuria, usually intermittent, often gross and occasionally with clots Pain is not a prominent symptom A local mass may be palpable generally not because of the pelvic neoplasm but as a result of the obstructive hydronephrosis The association of renal pelvic tumors, especially nonpapillary carcinomas, with calculi and infection is common (Kretschmer) Calculi and infection lead to, or are at least associated with, leukoplakia of the renal pelvis Leukoplakia of the renal pelvis, as in the case of other mucous membranes, frequently precedes the development of carcinoma (plates 310A, 311A)

*Special features*

There are two features of tumors of the renal pelvis that deserve special emphasis

1 Papillary carcinomas may appear deceptively benign, and

2 Papillary neoplasms of the renal pelvis are commonly associated (from 28 8 to 50 per cent, Cabot and Allen; Caulk) with similar tumors in the ureter and bladder, and may be bilateral In other words, the finding of a papillary tumor of the bladder, especially near *either ureteral orifice is sufficient basis to search for* similar tumors in *either* of the ureters and renal pelves The reason for the association is probably a neoplastic diathesis of the mucosa of the urinary tract with multicentric origin of the tumors, rather than implantation through direct or lymphatic seeding In any case, the multiplicity of the papillary lesions in the renal pelvis and ureter is so frequent that nephrectomy for pelvic tumors should be accompanied by total ureterectomy, preferably with removal of a cuff of bladder about the ureteral opening The association of pelvic, ureteral and bladder lesions is uncommon in the case of nonpapillary carcinomas of the renal pelvis and in renal parenchymal tumors

*Prognosis*

The main renal vein, its principal tributaries and the lymphatics are involved in a high percentage of cases Such involvement appreciably worsens the prognosis, as does a high histologic grade of the tumor Arterial invasion is rare

The prognosis of the papillary tumors without apparent infiltration is poor enough to em-

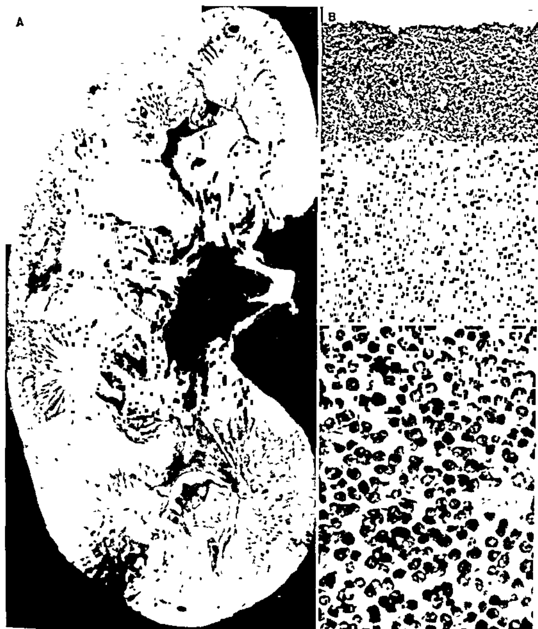



FIG A *Myelogenous leukemia* with grey and hemorrhagic areas of leukemic infiltration The pelvis is discolored by spontaneous intramucosal hemorrhage which may simulate neoplasms on pyelography

FIGS B AND C *Myelogenous leukemia* in low and high power magnification respectively Figure B superficially simulates subacute pyelonephritis Detailed study of the cells under higher magnification reveals their leukemic nature




FIG A *Myelogenous leukemic infiltrate* in interstitium of kidney showing pleomorphism, granularity of cytoplasm and mitotic activity

FIG B *Myelogenous leukemia* simulating subacute proliferative glomerulonephritis. The increased glomerular cellularity is due to the presence of leukemic cells in the glomerular capillaries.

FIG C *Hyaline granules* in the epithelium of the proximal tubules in association with leukemic infiltrate This hyaline granule nephrosis is identical with that in other conditions.

FIGS D AND E *Fibrinoid degeneration* of afferent arterioles and interlobular arteries is occasionally found in leukemic kidneys and is *unrelated* to hypertension or systemic vascular sclerosis This change has been attributed to $P^{32}$ (Platt) which was used in this case.




FIGS A AND B *Lymphatic leukemic infiltration* of kidneys

FIG C *Lymphatic leukemic infiltration* superficially simulating acute diffuse interstitial nephritis The glomeruli and tubules, although surrounded by the leukemic infiltrate seem to be structurally intact Despite the extensive leukemic involvement of the kidneys, there was no renal insufficiency, this is almost always the case




FIG. A. *Lymphosarcomatous infiltration* of renal parenchyma and perirenal tissues

FIG. C *Lymphosarcomatous envelope* tightly wrapped about kidney The parenchyma is also involved

FIG. B. *Periglomerular and interstitial lymphosarcomatous infiltrate.*

FIG. D *Lymphosarcomatous infiltrate* of parenchyma and capsule with some resemblance to a focus of subacute pyelonephritis.

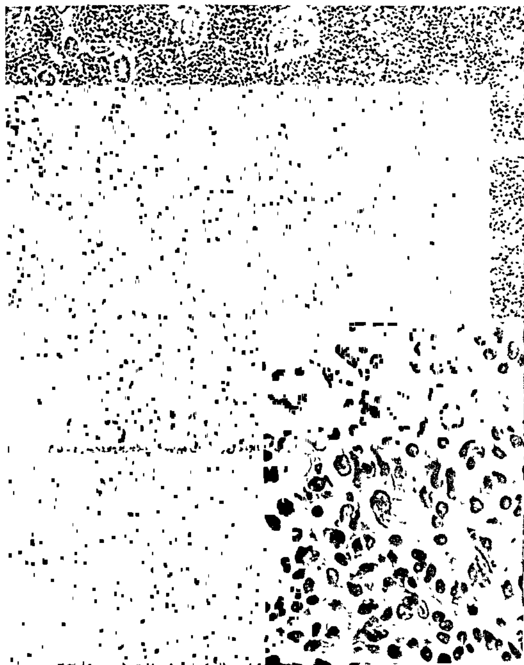



FIG A *Lymphosarcomatous infiltrate* with preservation of tubular structure The histologic picture is quite like that of lymphatic leukemia

FIG B *Mycosis fungoides*, a small focus in the kidney This is a most unusual finding in proved cases of mycosis fungoides

FIG C *Mycosis fungoides*, a higher magnification of figure B, showing the pleomorphism of the infiltrate

phasize that the failure to find infiltration is no insurance of survival In a series of McDonald and Priestley, only 13 of 25 patients with such tumors survived five years In other words, the noninfiltrating papillary tumors of the renal pelvis, that is, the "papillomas," *are of far* greater concern than the corresponding tumor of the urinary bladder Since approximately half of the patients with renal "papillomas" do not survive five years, it appears likely that by the time the tumor has been removed, infiltration has already occurred The difficulty is that histologic evidence of infiltration may be completely masked in a given section The case il*lustrated in plate 312 emphasizes this feature* rather strikingly Hence, the "papilloma" of the renal pelvis had better not be regarded as a benign lesion from the practical viewpoint

The prognosis of the remainder of the pelvic tumors is especially poor In the series of McDonald and Priestley, 3 of 18 patients with the obviously infiltrating papillary carcinomas, survived five years or longer, and only 1 of 14 *patients having nonpapillary lesions* was alive after five years. Higgins in 1939 was unable to find a single reported instance of five year survival of a case of squamous cell carcinoma of the renal pelvis The over-all prognosis for tumors of the renal pelvis is therefore far worse than for those of the parenchyma

## Mucous Adenocarcinoma of the Renal Pelvis

### *Definition*

Inasmuch as the renal pelvis as well as the ureter and bladder is lined by stratified transitional cell *epithelium, most of the neoplasms* arising from the renal pelvis are expected to be of the transitional or squamous cell types Metaplasia of the normal transitional epithelium into the squamous cell pattern is a common reaction in the presence of infection or stones which are frequently found with pelvic tumors. A similar metaplasia occurs in other organs such as the urinary bladder, the gall bladder and the lungs However, the prosoplastic conversion of the transitional cell epithelium of the renal pelvis into the more specialized, mucus producing epithelium of the type that occurs in the colon, is an exceedingly rare phenomenon. By this same token, mucous adenocarcinomas of the renal pelvis are correspondingly rare

Up to 1950, only two instances of mucous *adenocarcinoma of the renal pelvis* had been reported (Ragins and Rolnick, Ackerman) and a third case of mucinous metaplasia of the pelvis and part of the ureter is on record (Plaut). The ages of the patients with carcinoma were 51 and 66, the patient with simple metaplasia was 58 years old. Hydronephrosis with chronic pyelonephritis was present in all three cases, calculi were noted in all of the cases, metastasis *occurred in one case (Ackerman).*

The *histologic picture* of the carcinoma is identical with those that arise from the vestigial urachal cysts at the fundus of the bladder and is indistinguishable from gelatinous or mucous adenocarcinomas of the large intestine (plate 315) There is a temptation to indulge in the discussion of the possibly dysontogenetic nature of the intestinal type of glandular epi*thelium within the renal pelvis. Actually this* is the same kind of epithelium that is commonly found in the urinary bladder with exstrophy. In this circumstance, the alteration is logically assumed to be the result of the exposure of the mucous membrane of the exstrophied bladder to adverse conditions with which it is not "intended" to cope. The calculi and infections may similarly provoke a change to mucus producing epithelium in the pelvis, instead of the expected epidermalization, in rare instances.

The origin of mucus producing intestinal type of epithelium from Brunn's glands or from *pyelitis cystica are other possibilities that could* be invoked However, an examination of the altered renal mucosa indicates a thorough, intrinsic conversion of the entire epithelium in the involved areas rather than a mucous conversion merely of cysts of the Brunn's nests or of the intraepithelial foci of pyelitis cystica (plate 190).

## Pararenal Tumors

In view of the variety of pararenal tumors that occurs, it appears that the pararenal tissues have a greater propensity for neoplastic pro-

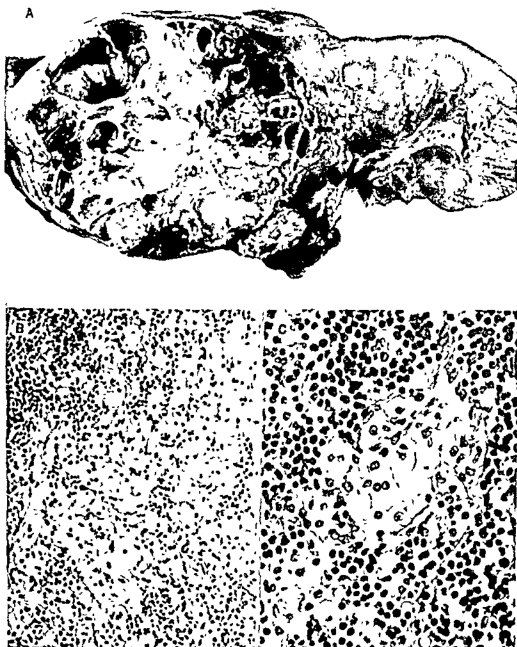
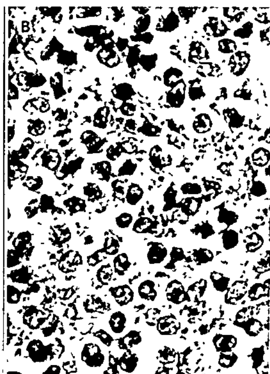



FIG A *Adenocarcinoma (clear cell), intimately combined with lymphosarcoma*, an unusual occurrence further illustrated below The patient had generalized lymphosarcomatosis

FIGS B AND C *Clear cell adenocarcinoma admixed with lymphosarcoma* These sections are from the tumor illustrated in figure A



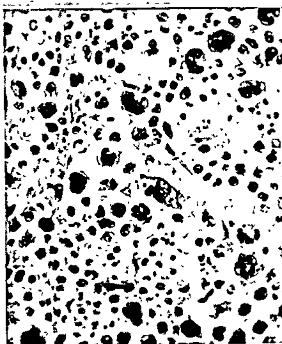







FIG A *Reticulum cell sarcoma* of kidney (grey focus—arrow)

FIG B *Typical pattern* of fairly uniform reticulum cell sarcoma of kidney.

FIG C *Giant reticulum cell sarcoma* which may be indistinguishable from Hodgkin's sarcoma in a single section

FIG D *Reticulum cell sarcoma* of kidney in an atypical pattern, and therefore, easily confused with adenocarcinoma

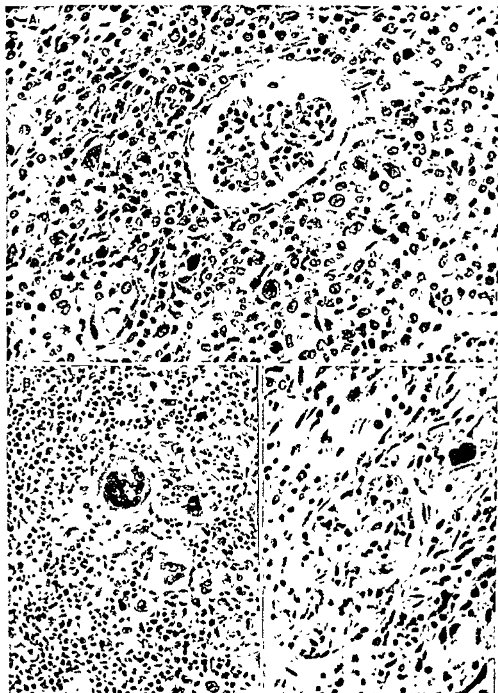
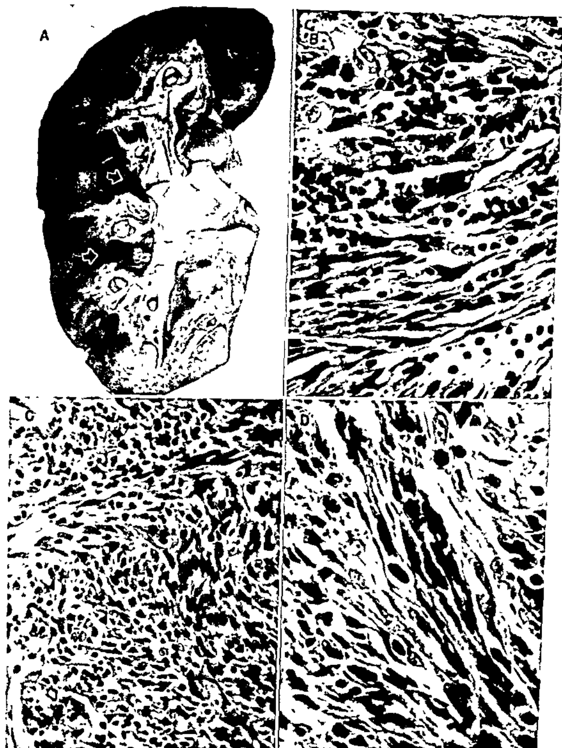



Fig A *Hodgkin's sarcoma of kidney*

Fig B *Hodgkin's granuloma* of kidney

Fig C *Hodgkin's granuloma* of kidney




FIGS A, B, C AND D *Variants of Kaposi's sarcoma* showing abortive blood vessels lined by neoplastic cells, granules of hemosiderin and anaplastic compact spindle cells Gross nodules are shown in figure A (arrows)



FIG A *Angiomyosarcoma* with many lipid histiocytes

FIG B *Another section* of the angiomyosarcoma of figure A Metastasis from this type of neoplasm is most unlikely

FIGS C AND D *Hemangiopericytoma of kidney* with metastases in pituitary gland and liver (biopsies) No cutaneous lesions were present The question of site of origin of this tumor was not settled in this case in which no autopsy was performed

liferation than the tissues surrounding other viscera with the possible exception of the lung The tissues normally consist of adipose, fibrous, vascular, muscular and neural elements and *corresponding tumors of these tissues occur*. There are lipomas, fibromas, myxomas, angiomas, lymphangiomas, and compounded tumors such as angiomyolipomas, fibrolipomas, myxolipomas as well as their sarcomatous counterparts (plates 316, 317). Pararenal teratomas occur rarely (Campbell, Baker and Ragins) Metaplastic ossification or chondrification may be mistaken for teratomatous components The most common of the pararenal tumors are the various lipomas (Pemberton and McCaughan) Occasionally, a pararenal lipoma may so distort the renal pelvis as to suggest an intrapelvic tumor Neoplasms may arise from perinephric tissues which seem not to be indigenous to this region but which are in reality metaplastic derivations. The osteogenic sarcoma pictured in plate 330 is a case in point Other examples of extra-osseous osteogenic sarcoma have been recorded (Binkley and Stewart; Weber) They are relatively benign tumors As already mentioned, some of the largest neoplasms of the entire body have originated from the perinephric tissues and have reached weights of 60 to 69 pounds (Gordon-Taylor) The symptoms have been those resulting from compression.

It is curious that there is a higher incidence of pararenal tumors among females than males The ratio in von Wahlendorf's series was 106 females to 42 males. The tumors may be found at all ages and both sides are affected equally. Local recurrences following operative removal are more common than would be anticipated from the histologic picture of some of the tumors, although portions of a lipoma may undergo sarcomatous degeneration (plate 317B), at least in the purely histologic sense.

### *Peripelvic Lymphatic Cysts*

#### *Solitary*

Solitary peripelvic cysts have been called "lymphatic cysts" by some observers These are rare and usually small, although huge ones with a volume of one to five liters have been described. The larger ones obviously would cause symptoms of compression In several instances, hypertension has been attributed ischemia caused by the pressure of the cyst the renal vessels Removal or drainage of t cyst in these cases is said to have been follow by a sustained fall in blood pressure (Sch Kreutzmann).

#### *Multicystic*

In addition to the solitary cysts, there occ multiloculated or honey-combed hilar pe pelvic, pericalyceal or pyramidal cysts (pla 316A). These cysts are not rare, occurring over 1 per cent of routine autopsies in patien from 17 to 71 years of age and about four tim as commonly in males as in females (He thorne) The majority of the patients in He thorne's series had some associated obstructi or inflammatory disease of the kidney includir nephrolithiasis, pyelonephritis and prostat hypertrophy. On this basis, acquired obstru tive lymphangiectasis might be considered th most likely pathogenesis of the cysts If ob struction of lymphatic drainage is the cause c lymphangiectasis, it is surprising that man more examples are not found especially in th cases of extensive cancerous compression of ure teral and renal lymphatics. However, 8 of th 20 cases had associated, possibly congenita malformations, some of which were probabl embryogenetically much alike, these include pancreatic and hepatic cysts, hemangioma o the ileum, liver and spleen, and "lymphangi oma" of the spleen. Nevertheless, the observation of these cysts mostly beyond the second decade of life suggests an acquired rather than congenital origin As with cysts elsewhere in the kidney and in other organs, the theories of genesis run the gamut of dysontogenetic manipulation, of which the theory of origin from remnants of the wolffian body appears to have won many adherents.

The multiple cysts may be visible, without sectioning the kidney, as bosselated masses about the size of lymph nodes lobulating the peripelvic fat The photograph in Henthorne's paper demonstrates this feature well. The sectioned surface reveals pelvic or pericalyceal thin-walled cysts varying in size from those barely detectable to some 5 cm in diameter, but averaging about 1 cm. The lining of the cyst

## PLATE 328. Malignant Neoplasms: Metastatic Tumors

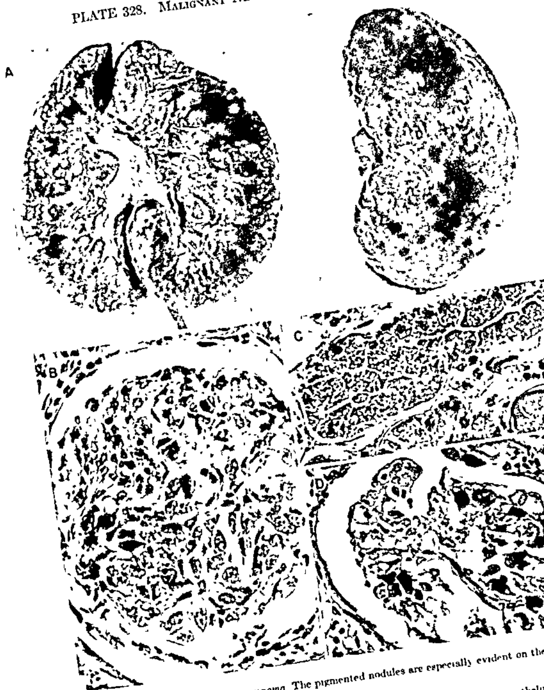



Fig A *Metastatic melanocarcinoma* The pigmented nodules are especially evident on the [...]lar surface.

B *Glomerular metastasis* of melanocarcinoma.

Fig C *Melanin granules* in epitheli[...] convoluted tubules in a case of wid[...] pigmented melanocarcinoma

Fig D *Metastatic cells* of mela[...] [...]lar capillaries (Compare wi[...]

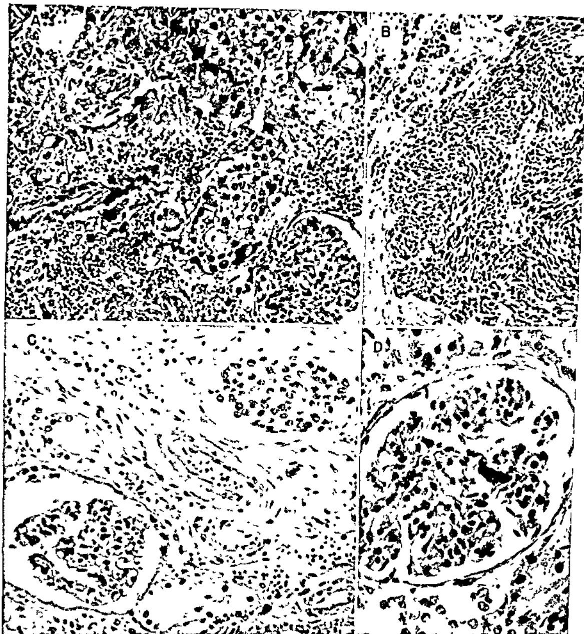



FIG A *Metastatic choriocarcinoma* to kidney Langhans and syncytial cells and the hemorrhagic character of the tumor are noted

FIG B *Metastatic epidermoid carcinoma* from the lung, which may be mistaken for a primary, renal pelvic carcinoma (plate 311B)

FIG C *Metastatic epidermoid carcinoma* (from the ureter) within a renal lymphatic vessel.

FIG D *Megakaryocyte* within a glomerular capillary, a common finding not to be confused with a metastatic cancer cell




FIG A *Extra-osseous osteogenic sarcoma* originating in the perirenal tissue

FIG B *Perirenal osteogenic sarcoma* with foci osteogenesis and spindle cell areas

FIGS C AND D *Perirenal extraosseous osteogenic sarcoma* with new bone and giant cell formation in a malignant stroma There were no metastases The *extraosseous* osteogenic sarcomas in general, have a far better prognosis than those arising within bones

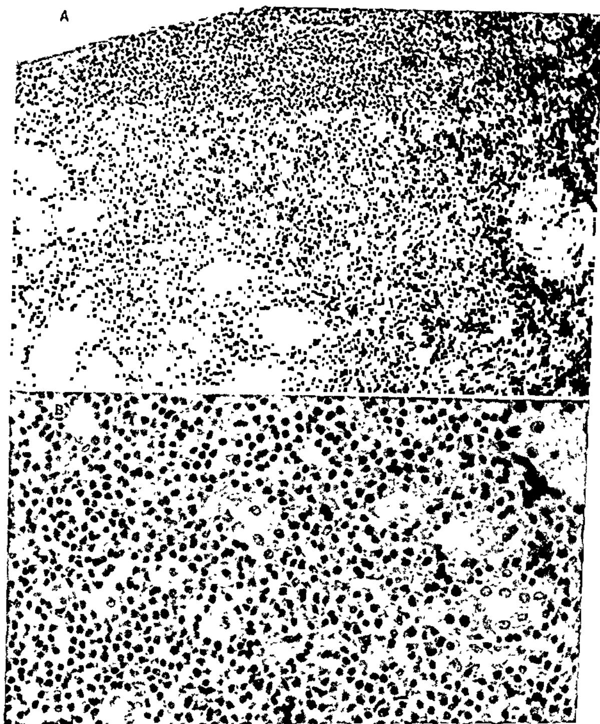
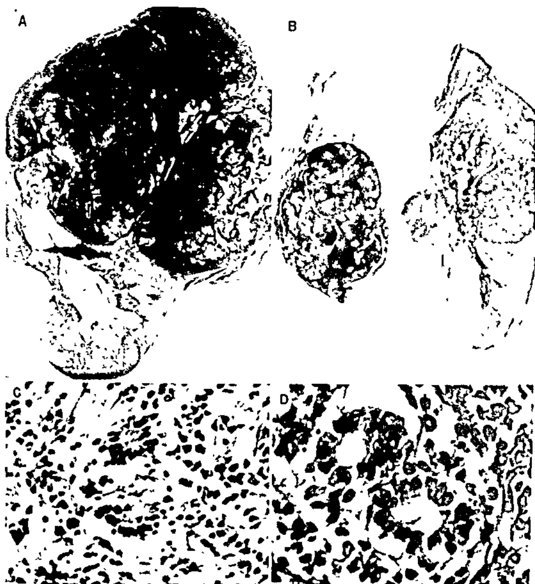



FIG A *Myelosarcomatous (multiple myeloma, plasmacytoma) growth within kidney* from a case of widespread myelomatous involvement of bones

FIG B *Myeloma (plasmacytoma)* of kidney of figure A under higher magnification There was no evidence of myeloma nephrosis in this case (Compare plates 149–151)




FIGS A AND B *Adrenal neuroblastoma* directly invading the adjacent renal parenchyma and easily mistaken for a primary renal neuroblastoma

FIG C *True rosettes* of an adrenal neuroblastoma

FIG D *Tubular structures* of a Wilms' tumor simulating true rosettes for which they may be mistaken

is smooth and the contents comprise a clear serous fluid Nothing concerning the position of the cysts in anatomic relation to blood vessels militates against their lymphatic nature Histologically, the wall of the cysts is made up of flattened lining cells about which there is a thin rim of fibrous tissue or smooth muscle, as in a vein or lymphatic In the three cases we have personally seen, we were not able to know from the histologic sections whether or not the cysts were dilated lymphatics or veins It is also to be noted that there occur isolated multilocular peripelvic cysts which appear to be dilated isolated foci of tubules or tubular remnants rather than lymphatic cysts

### *Lymphangioma*

A true lymphangioma, to be distinguished from lymphangiectasis, or multiloculated lymphatic cysts, is a rare pararenal tumor The case reported by Kretschmer and Hibbs in 1934 is an excellent example of an encapsulated lymphangiomatous tumefaction about the size of an orange (11 x 9 x 8 5 cm ) which markedly distorted the kidney by compression The patient was 59 years of age At that time, they were able to find two other reports of such tumors adjacent to the kidney.

### Pararenal Hematoma

Pararenal hematoma results from spontaneous rupture of a sclerotic aorta (plate 316C) or main renal artery with or without prior aneurysmal dilatation, massive adrenal hemorrhage (adrenal "apoplexy"), hemorrhage from retroperitoneal tumors, blood dyscrasias, trauma, and from extensions of intrarenal hemorrhage secondary to periarteritis nodosa (plate 228B), lithiasis, hydronephrosis, infarcts, cysts and neoplasms. In some instances, the cause of the hemorrhage escapes detection

The onset of the pararenal hematoma is characterized by sudden, severe, intermittent, shooting pain in the flank followed often by [illegible]

[illegible] clinical differential diagnosis may be difficult to make since the picture may simulate an intra-abdominal catastrophe, renal lithiasis, cholelithiasis, or perforation of the gallbladder.

### Metastasis

The kidney is a relatively common site for the deposit and propagation of metastases. Those primary tumors that are prone to give rise to widespread metastases, are likely also to seed foci in the kidney Among such tumors are bronchogenic carcinomas (plate 329B), malignant melanomas (plate 328), choriocarcinomas (plate 329A) and the various lymphomas (plates 318–325) These may rarely involve the renal pelvis in addition to the parenchyma. However, the kidney receives metastases also from many other primary neoplasms, including especially those from breast, pharynx, larynx, opposite kidney, thyroid, stomach, skin, pancreas, liver, esophagus, large intestine, adrenal neuroblastoma and others The adrenal gland (33 per cent), lungs (18 per cent), thyroid gland (15 per cent) and opposite kidney (12 per cent) are the chief sources of metastasis. The routes of spread of tumors to the kidney are:

1. Direct contiguous invasion
2. Lymphatic (retrograde)
3. Venous (retrograde)
4. Arterial

The organs responsible for *direct spread* of cancers to the kidney include stomach, pancreas, adrenals (with cortical and medullary tumors) (plate 332), and large intestine. Occasionally, the kidney may be invaded by direct extension from an adjacent lymph node which is itself occupied by some metastatic lesion. As in other regions in which there is a tough fibrous capsule, the renal capsule may effectively bar the penetration into the renal parenchyma of even highly anaplastic pararenal cancers.

Invasion of the kidney by retrograde permeation of the *lymphatic* vessels is especially common with anaplastic epidermoid carcinoma of the renal pelvis. The lymphatic deposits in this instance may be so atypical as to simulate adenocarcinoma, reticulum cell sarcoma, myosarcoma or Wilms' tumor (plate 311B). Such extensive intrarenal lymphatic spread may be seen also in cases of carcinoma of the stomach,




FIG. A. *Adrenal neuroblastoma* metastatic to kidney.

FIG. B. *True rosettes* of a metastatic adrenal neuroblastoma.

FIGS. C AND D. *Wilms' tumor* with multinucleated giant cells deceptively similar to true rosettes.

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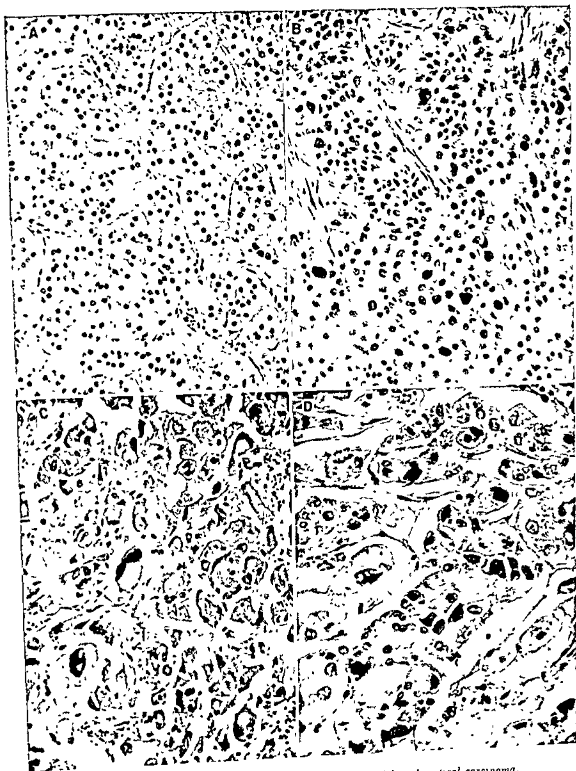



FIG A *Adrenal cortical adenoma*

FIG B *Adrenal cortical carcinoma.*

FIG C *Pheochromocytoma* of adrenal medulla

FIG D *Renal adenocarcinoma* simulating a pheochromocytoma

pancreas, lung, and gall bladder. The lymphatic invasion may be so complete in these instances as to indicate the actual anatomical pattern of the renal lymphatics (Peirce).

*Retrograde invasion of renal veins* and their intrarenal tributaries has been observed with ovarian and contralateral renal carcinomas and with other neoplasms which have extended first into the inferior vena cava. *Arterial embolic metastases* are of frequent occurrence. They may be so large as to occlude a major branch and thereby produce an infarct Frequently, arterial metastases lodge within glomerular capillaries and, when sparse, may easily be overlooked (plate 328B) As a rule, the metastatic foci are visible grossly as spherical, lentiform or rhomboidal nodules of various sizes The nonspherical metastases tend to have their longer axis parallel to the rays of the kidney because of the natural cleavage planes; others may have their shape moulded into a pyramidal or conical form by the limitation of the capsule (Willis) Metastases rarely reach very large dimensions, and, in part for this reason, they infrequently undergo extensive spontaneous necrosis Incidentally, metastatic foci of adenocarcinoma may lodge in Bowman's space and be misinterpreted as hyperplastic and hypertrophic parietal epithelium of Bowman's capsule

It is remarkable that despite overwhelming involvement by metastases, or particularly lymphomas, the function of the kidney is rarely seriously compromised thereby Histologically, the glomerular and tubular structures may appear quite intact though enveloped by neoplastic tissue (plate 325). It is extremely uncommon, for example, for patients with massive parenchymal lymphomatous infiltrate in the kidney to develop an associated hypertension even though one might anticipate an ischemic compression of small renal arteries and arterioles by the tumor Infrequently a large metastasis at the renal hilum encroaching on the main vessels, or a metastatic lesion obstructing the ureter may play a part in the development of hypertension or hydronephrosis

REFERENCES


ACKERMAN, L V Mucinous adenocarcinoma of the pelvis of the kidney J Urol 65: 36–45, 1946

BAKER, W J, AND RAGINS, A B Pararenal teratoma case report J Urol 63: 982–990, 1950

BARNEY, J D, AND CHURCHILL, E D Adenocarcinoma of kidney with metastasis to lung cured by nephrectomy and lobectomy J Urol 42: 269–276, 1939

BEER, E Some aspects of malignant tumors of the kidney Surg, Gynec & Obst 65. 433–446, 1937

BELL, E T A classification of renal tumors with observations on the frequency of various types J Urol 39 238–243, 1938

— Renal Diseases Philadelphia, Lea and Febiger, 1946

BINKLEY, J S, AND STEWART, F W · Morphogenesis of extraskeletal osteogenic sarcoma and pseudo-osteosarcoma Arch Path 29: 42–56, 1940

BONNECARRERE, E A · Phlebothrombosis in tumors of the kidney J Urol 63: 451–458, 1950

B[illegible]

B[illegible] renal cytology J Urol 63: 464–474, 1950

CABOT, H, AND ALLEN, R B, Epithelioma primary in the renal pelvis, report of 45 cases Lancet, 2: 1301-1306, 1933

CABOT, H, AND MIDDLETON, A W Relation of so-called adenoma of kidney to carcinoma of kidney Tr Am A Genito-Urin Surgeons 31: 91–105 1938

CAHILL, G F, AND MELICOW, M M. Calcification of renal tumors and its relation to prognosis J Urol 39. 276–286, 1938

CAMPBELL, M F Pararenal teratoma in an infant, case report J Urol 29 677–684, 1933

CAULK, J R Tumors of the renal pelvis and ureter Ann Surg 106· 68–84, 1937

COOKE, W E Malignant leiomyoma of kidney J [illegible]

[illegible] phroma in adults, a clinico pathologic study of Wilms' tumors and related renal neoplasms J Urol 60. 552-576, 1948

DANIEL, W. E Hypertensive factor in Wilms' tumor. South M J 32· 1014–1016, 1939

DAVISON, C, BROCK, S, AND DYKE, C G · Retinal and central nervous hemangioblastomatosis with visceral changes (von Hippel Lindau's disease) Bull of Neurol Inst New York 5: 72–93, 1936

DEAN, A, AND PACK, G T · Embryonal adenosarcoma of kidney. J A M A 98: 10-17, 1932.

DORMAN, H N, AND FOWLER, H A. Hemangioma of the kidney, report of an additional case. J. Urol 55: 348-357, 1946

FOOT, N C, AND PAPANICOLAOU, G. N Early renal carcinoma in situ J A M. A 139: 356-358, 1949

FOULDS, G S, AND SCHOLL, A J Squamous cell tumors of renal pelvis Ann Surg 80: 594-605, 1924

FROUG, C Liposarcoma of kidney, review of literature and case report. J Urol 45: 290-295, 1941

GORDON, B S Tubular adenoma of the kidney J Urol 59: 1019-1021, 1948

GORDON, M P, JR, KIMMELSTIEL, P, AND CABELL, C L Leiomyoma of kidney, report of case with review of literature J Urol 42· 507-519, 1939

GORDON-TAYLOR, G Gigantic benign tumor of kidney weighing 22 pounds Nephrectomy. cure Brit J Surg 17: 551-554, 1929-30

HAMER, H G, AND WISHARD, W N, JR Osteogenic sarcoma involving right kidney J Urol. 60: 10-17, 1948

HARRIS, A Retroperitoneal angioma, review of literature on perirenal tumors J Urol 21: 181-192, 1929

HAWM, F C, AND DE VEER, J A Fatty replacement following renal atrophy or destruction, so-called lipomatosis of kidney J Urol 41: 850-866, 1939

HENTHORNE, J C Peripelvic lymphatic cysts of the kidney, review of literature on perinephric cysts Am J Clin Path 8· 28-38, 1938.

HIGGINS, C C Squamous cell carcinoma of the renal pelvis Arch Surg 38: 224-244, 1939

—— Adenoma of the kidney, report of six cases Am J. Surg 65: 3-14, 1944

HYMAN, A A clinical study of malignant tumors of the kidney S Clin North America 13: 347-364, 1933

JACOBS, P A, AND ROSENBERG, W Telangiectasis of kidney simulating renal tumor J Urol 17: 337-343, 1927

JUDD, E S, AND DONALD, J M Sarcoma of the kidney of the adult Arch Surg 96: 1028-1031, 1932

KILLINGSWORTH, W P Cartilage in the kidney. Arch Path 47: 487-493, 1949

KIMBALL, F N, AND FERRIS, H W Papillomatous tumors of renal pelvis associated with similar tumors of ureter and bladder, review of literature and report of 2 cases J Urol 31: 257-304, 1934

KIRKMAN, H, AND BACON, R L Malignant renal tumors in male hamsters (Cricetus auratus) treated with estrogen Cancer Research 10. 122-123, 1950

KRETSCHMER, H L · Non-papillary carcinoma of the renal pelvis J. Urol 1: 405-436, 1917.

—— Adenomyosarcoma of kidney (Wilms' tumor), report of 3 cases Arch Surg 41: 370-384, 1940

——, AND HIBBS, W. G. Mixed tumors of the kidney in infancy and childhood Surg, Gynec, & Obst. 52: 1-24, 1931.

—— AND ——: Retroperitoneal perirenal lymphangioma Arch Surg 29: 113-125, 1934

KREUTZMANN, H A. R · Hypertension associated with solitary renal cyst; report of 2 cases. J. Urol. 57: 467-472, 1947.

LADD, W E: Embryoma of kidney (Wilms' tumor) Ann Surg. 108: 885-902, 1938

LEARY, T Crystalline ester cholesterol and adult cortical renal tumors Arch Path 50: 151-178, 1950

LOWNES, J B, BARON, S, AND LIPSCHUTZ, H · Hemangioma of the kidney, report of 2 cases J Urol 58: 417-423, 1947.

LUBARSCH, O · Die Nierengewächse In Handbuch der speziellen pathologischen Anatomie und Histologie Henke, F, and Lubarsch, O, Vol VI, pt 1, chapt 8, pp 586-720, Berlin, J Springer, 1925

MACALPINE, J B · Papillomatous disease of renal pelvis Brit J. Surg 35: 113-132, 1947.

—— Bilateral renal papillomata, 2 cases Brit J. Surg 35: 132-134, 1947.

MCCARTNEY, J S, AND WYNNE, H M. N: Liposarcoma of kidney Am J. Cancer 26: 151-154, 1936

MACDONALD, E J · The present incidence and survival picture in cancer and the promise of improved prognosis Bull Am. Coll. Surgeons 33: 75-93, 1948

MCDONALD, J R, AND PRIESTLEY, J. T. Carcinoma of renal pelvis, histopathologic study of 75 cases with special reference to prognosis. J Urol 51: 245-258, 1944

MANN, L T Spontaneous disappearance of pulmonary metastases after nephrectomy for hypernephroma, four year follow-up J Urol 59: 564-566, 1948

MARSHALL, V F The occurrence of endometrial tissue in the kidney, case report and discussion J Urol 50. 652-656, 1943

MASLOW, L A Wilms' tumor, report of 3 cases and possible fourth one in same family J. Urol 43: 75-81, 1940

MASSON, P The role of the neural crests in the embryonal adenosarcomas of the kidney Am J. Cancer 33: 1-32, 1938.

MELICOW, M M Classification of renal neoplasms, a clinical and pathological study based on 199 cases J Urol 51: 333-385, 1944

MITCHELL, N, AND ANGRIST, A: Adrenal rests in the kidney Arch Path 35· 46-52, 1943.

MOOLTEN, S E. Hamartial nature of the tuberous sclerosis complex and its bearing on the tumor problem Arch Int Med. 69: 589-623, 1942

NEFF, J H: Massive hemorrhagic cyst in Wilms' tumor of kidney in adult Tr. Am A Genito-Urin Surgeons 24: 1-12, 1931.

NEWMAN, B, AND REED, T.. Liposarcoma of the kidney· report of a case. J. Urol. 62: 292-294, 1949.

O'Crowley, C R, and Martland, H S: Adrenal heterotopia, rests, and the so-called Grawitz tumor J Urol 50: 756-768, 1943

Ostrum, H W, and Fetter, J. S Silent nephroma J Urol 43 39-51, 1940

Owen, C I Glomeruloma of the kidney with report of case and review of literature. J Urol 8: 302-314, 1938

Papanicolaou, G. N, and Marshall, V F Urine sediment smears as a diagnostic procedure in cancers of the urinary tract Science 101: 519-520, 1945

Peirce, E C Renal lymphatics Anat Rec 90. 315-329, 1944

Pemberton, J deJ, and McCaughan, J M Intrarenal and perirenal lipomata Surg, Gynec, & Obst 56 110-115, 1933

Pfeiffer, G E, and Gaudin, M M Massive perirenal lipoma with report of a case J Urol 56: 12-27, 1946

Platt, W R: Effects of radioactive phosphorus ($P^{32}$) on normal tissues Arch Path 43: 1-14, 1947

Plaut, A Diffuses dickdarmähnliches Adenom des Nierenbeckens mit geschwulstartiger Wucherung von Gefässmuskulatur Ztschr f urol Chir 26 562-578, 1929

Popper, H, and Ragins, A B Histologic demonstration of Vitamin A in tumors Arch Path 32. 258-271, 1941

Priestley, J T Survival following removal of malignant neoplasms J A M A 113: 902-906, 1939

——, and Schulte, T L Treatment of Wilms' tumor J Urol 47: 7-10, 1942

Prince, C L Primary angioendothelioma of kidney, report of case and brief review J Urol 47. 787-792, 1942

Ragins, A B, and Rolnick, H C Mucus producing adenocarcinoma of the renal pelvis J Urol 63. 66-73, 1950

Robertson, T D, and Hand, J R Primary intrarenal lipoma of surgical significance J Urol 46: 458-474, 1941.

Scholl, A J Perinephric lymphatic cysts of kidney, report of 2 cases J A M A 136. 4-7, 1948

Sparks, A J Wilms' tumor in a 63 year old male, case report J Urol 47 642-647, 1942

Sporer, A, and Pollock, R Renal varix J. Urol 58 424-427, 1947

Staff of St Vincent's Memorial Hospital The Cytologic Diagnosis of Cancer Philadelphia, Saunders, 1950

Valentine, J J Dermoid cyst of the kidney Am J Surg 6 93-97, 1929

von Wahlendorf, A R L Ueber retroperitoneale Lipome Arch f klin Chir 115: 751, 1921

Weber, F P Osteochondrosarcoma enclosing left kidney and suprarenal glands in a girl aged 15 years Brit J Child Dis 28 136-138, 1931

Willis, R A The Spread of Tumours in the Human Body London, J & A Churchill, 1934

Wilms, M Die Mischgeschwulste der Niere Leipsig, A Georgi, 1899

Wilner, S Large perirenal angiosarcoma Am J Surg 34 168, 1920

Wilson, A A Accessory adrenal cortical tissue Arch Path 27. 955-965, 1939

Wood, D A Adenomyosarcoma of kidney in adult (Wilms' tumor), report of case J Urol 51 235-244, 1944

DEAN, A, AND PACK, G. T · Embryonal adenosarcoma of kidney J A M A 98: 10–17, 1932
DORMAN, H N, AND FOWLER, H A. Hemangioma of the kidney, report of an additional case J Urol. 55: 348–357, 1946
FOOT, N C, AND PAPANICOLAOU, G N Early renal carcinoma in situ J A M A 139: 356–358, 1949.
FOULDS, G S, AND SCHOLL, A J Squamous cell tumors of renal pelvis Ann Surg 80: 594–605, 1924
FROUG, C Liposarcoma of kidney, review of literature and case report J Urol 45: 290–295, 1941
GORDON, B S Tubular adenoma of the kidney J Urol 59: 1019–1021, 1948
GORDON, M P, JR, KIMMELSTIEL, P, AND CABELL, C L Leiomyoma of kidney, report of case with review of literature J Urol 42: 507–519, 1939
GORDON-TAYLOR, G Gigantic benign tumor of kidney weighing 22 pounds Nephrectomy cure Brit J Surg 17: 551–554, 1929–30
HAMER, H G, AND WISHARD, W N, JR Osteogenic sarcoma involving right kidney J Urol 60: 10–17, 1948
HARRIS, A · Retroperitoneal angioma, review of literature on perirenal tumors J Urol 21: 181–192, 1929
HAWM, F C, AND DE VEER, J A Fatty replacement following renal atrophy or destruction, so-called lipomatosis of kidney J Urol 41. 850–866, 1939
HENTHORNE, J C Peripelvic lymphatic cysts of the kidney, review of literature on perinephric cysts Am J Clin Path 8: 28–38, 1938
HIGGINS, C C Squamous cell carcinoma of the renal pelvis Arch Surg 38: 224–244, 1939
—— Adenoma of the kidney, report of six cases Am J. Surg 65: 3–14, 1944
HYMAN, A A clinical study of malignant tumors of the kidney S Clin North America 13: 347–364, 1933
JACOBS, P A, AND ROSENBERG, W Telangiectasis of kidney simulating renal tumor J Urol 17: 337–343, 1927
JUDD, E S, AND DONALD, J M Sarcoma of the kidney of the adult Arch Surg 96: 1028–1031, 1932
KILLINGSWORTH, W P Cartilage in the kidney. Arch Path 47: 487–493, 1949
KIMBALL, F N, AND FERRIS, H W Papillomatous tumors of renal pelvis associated with similar tumors of ureter and bladder, review of literature and report of 2 cases J Urol 31: 257–304, 1934
KIRKMAN, H, AND BACON, R L Malignant renal tumors in male hamsters (Cricetus auratus) treated with estrogen Cancer Research 10: 122–123, 1950
KRETSCHMER, H L. Non-papillary carcinoma of the renal pelvis J Urol 1: 405–436, 1917.
——· Adenomyosarcoma of kidney (Wilms' tumor); report of 3 cases. Arch Surg 41: 370–384, 1940
——, AND HIBBS, W G Mixed tumors of the kidney in infancy and childhood. Surg., Gynec., & Obst 52: 1–24, 1931.
—— AND ——. Retroperitoneal perirenal lymphangioma Arch. Surg 29: 113–125, 1934
KREUTZMANN, H. A R.: Hypertension associated with solitary renal cyst; report of 2 cases J. Urol. 57: 467–472, 1947
LADD, W E: Embryoma of kidney (Wilms' tumor) Ann Surg 108: 885–902, 1938
LEARY, T Crystalline ester cholesterol and adult cortical renal tumors Arch Path. 50 151–178, 1950
LOWNES, J B., BARON, S., AND LIPSCHUTZ, H · Hemangioma of the kidney; report of 2 cases J Urol 58: 417–423, 1947
LUBARSCH, O: Die Nierengewächse In Handbuch der speziellen pathologischen Anatomie und Histologie Henke, F, and Lubarsch, O, Vol VI, pt 1, chapt 8, pp 586–720, Berlin, J Springer, 1925
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—— Bilateral renal papillomata; 2 cases Brit. J. Surg 35 132–134, 1947.
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MOOLTEN, S E Hamartial nature of the tuberous sclerosis complex and its bearing on the tumor problem Arch Int Med 69· 589–623, 1942
NEFF, J H · Massive hemorrhagic cyst in Wilms' tumor of kidney in adult Tr. Am. A Genito-Urin Surgeons 24: 1–12, 1931
NEWMAN, B, AND REED, T Liposarcoma of the kidney report of a case J. Urol 62: 292–294, 1949

# 15. Histologic Artefacts

A CLEAR understanding of the nature, mechanism of production, and differential histologic diagnosis of artefacts is frequently of considerable importance. The misinterpretation of factitious changes has led to a number of erroneous conclusions some of which are fixed in the literature Many of these artefacts may be found in any organ, several of them, however, are limited to the kidney Most of the more significant ones are herein described and illustrated.

*Glomeruli*

Bowman's spaces occasionally appear abnormally enlarged and the tufts so conspicuously compressed as to simulate hydronephrotic atrophy simply as a result of shrinkage caused by formalin fixation, caution should be observed in the estimation of glomerular cellularity in thick *paraffin sections and especially in frozen* sections of kidneys The disparity between the cellularity of glomeruli in frozen sections in contrast with that of thin (4–6 microns) paraffin sections may be more striking than anticipated. Hence, the diagnosis of acute diffuse glomerulonephritis made on the basis of a frozen section at autopsy, may have to be retracted when the thin paraffin section is available

Another feature of poor fixation—particularly with formalin—is the tendency of the cytoplasm of the endothelial cells of the glomerular capillaries to swell and merge so as to give the impression, as a result of their acidophilic syncytium, that the basement membranes of the glomerular capillaries are thickened when they are actually normal.

More recently, significance has been attached to the so-called herniation of tubules into the glomerular or Bowman's space. It is admitted that in none of these instances is there evidence of embarrassment or alteration of the normal physiology or histology of the malpighian tuft such as would be expected by this sort of encroaching "lesion." Therefore, the artefactual genesis of this picture seems settled.

*Tubules*

One of the problems of the evaluation of alteration of tubular epithelium is the distinction between true degeneration and postmortem autolysis. Frequently, the change in the epithelium of the proximal convoluted tubules is labeled "necrotizing nephrosis," "infarct" or "ischemic necrosis" when the change is merely the result of postmortem alteration. The labile granular epithelium of the proximal c
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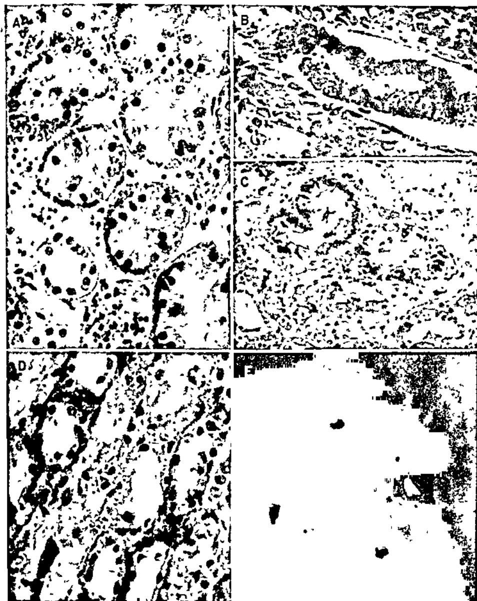



Fig A *Formalin pigment* in basilar portion of fatty epithelium of proximal tubules

Fig D *Silver granules* are to be differentiated from formalin pigment This example of renal argyrosis was the result of the ingestion of silver nitrate

Fig B *Formalin pigment* in distal convoluted tubule

Fig C *Hemosiderin* in proximal tubules is to be differentiated from formalin pigment

Fig E *Refractile foreign bodies*, such as dust in or upon the section, are to be differentiated from crystals deposited in vivo

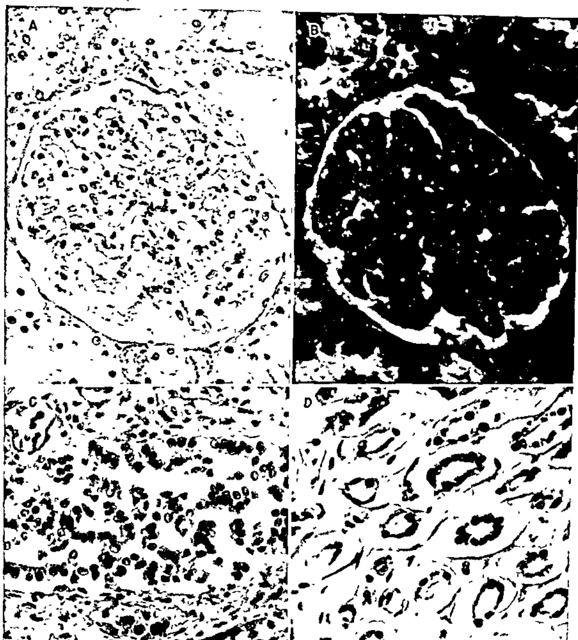



FIG A *Formalin pigment* in a glomerulus

FIG B *Refractile formalin pigment* in glomerulus of figure A

FIG C *Postmortem epithelial desquamation*

FIG D *Postmortem shrinkage of epithelium* from the tubular basement membrane (Formalin fixation)




FIG A *Postmortem degeneration of epithelium of proximal convoluted tubules* The more resistant glomeruli and the epithelium of the distal convoluted tubules survive a longer period The bland nonreactive disappearance of nuclei is characteristic of this phenomenon of postmortem change

FIG B *Uneven staining reaction* is due to an oily contaminant on the surface of the section or in the staining solutions




FIG A *Postmortem growth of bacteria* in glomerular capillaries Inflammatory reaction is absent

FIG B *Postmortem colonization* of staphylococci in peritubular capillaries

FIG C *Postmortem growth of monilia*

FIG D. *"Cysts"* due to postmortem accumulation of gas from growth of *Cl welchii*.

FIG E *Antemortem septic embolus* to afferent arteriole showing leukocytic reaction.

## PLATE 339. Histologic Artefacts of Kidney




Fig. A *Postmortem sloughing* of endothelial nuclei into lumen of an artery. The elongated cells simulate fibroblasts

Fig. B *Artefactually implanted tumor cells* in lumen of a vessel

Fig. C *Factitious invagination* of wall of elastic retractile artery may be mistaken for a thrombus

Fig. D *Blue black mercury pigment* from Zenker's fixative may be confused with calcium

Fig. E *Artefactual pseudosickling*

phenomenon." Because of the retractility of muscular, elastic arteries, their cut ends frequently telescope or invaginate so that when sectioned, they may histologically simulate true thrombosis so closely as to be fixed in the literature in this disguised form. This artefact should be recognized in the routine hematoxylin and eosin stained sections, but a simple van Gieson elastic tissue stain positively reveals the elastic lamina and media indicative of the artificial invagination which, in the past, has been labeled "a peculiar smooth muscle thrombus" (plate 339C)

Another less camouflaged artefact is that caused by the spindled endothelial cells and muscle cells of the media which have been forced into the lumen of arteries by the knife of the microtome (plate 339A) Such cells in the midst of blood and fibrin simulate fibroblasts and may be mistaken for organizing thrombi

Frequently red blood cells, in veins particularly, may appear sickled to the degree shown in plate 339E Precisely why this distortion occurs is not entirely clear, but its association with local anoxia merits further thought and investigation.

*Special Stains*

One of the most important bases for errors in the estimation of histologic changes in the kidney is the evaluation of special stains. Two principal types of errors are involved In one, the misjudgment results from the artefactual precipitation of the stain in adventitious locations. For example, the red carmine granules of the Best's stain for glycogen, the blue masses of the ferri-ferrocyanide or Prussian blue reaction for iron or hemosiderin, or the granules of reduced silver compounds may be precipitated unnaturally and may easily be mistaken for intravital reactions Similarly the localization of the various black sulfides ordinarily presumed to be reflective of the content of phosphatase, lipases or esterases (plate 24), may be varied by many artificial influences including heat, mechanical factors, and inhibiting chemical agents.

Not the least source of error is the brown to black granules of "formalin pigment." Formalin pigment appears to result from a reaction of formalin with hemoglobin and is deposited in organs fixed excessively long in solutions of formaldehyde The pigment is deposited particularly within or about areas of congestion as well as within lipid foci (plate 335) In glomeruli, the formalin may be mistaken for malaria pigment (plate 336A, B); in tubules, it closely approximates hemosiderin, melanin, or the lipochromes. Of course, the stains for iron are negative in the case of formalin pigment. Moreover, this pigment is most often birefringent (plate 336B), and can usually be bleached in sections treated with sodium carbonate Melanin may be bleached with permanganate or stained with silver The lipochromes of the kidney are sudanophilic With regard to the property of birefringence, it is to be borne in mind that particles of foreign matter caught within or above the section of tissue during its preparation, may also be anisotropic (plate 337E)

Occasionally, irregular areas of tissue may show no affinity for stains (plate 337B) This phenomenon may be due to the presence of droplets of an oily material on the section itself or actually contaminating oils within the aqueous staining solutions

*Postmortem Bacterial Invasion*

Occasionally it becomes a problem to distinguish between antemortem and postmortem colonization of bacteria The criterion that is of obvious importance is the presence or absence of inflammatory cellular reaction about the bacteria (plate 338). However, in cases of agranulocytosis or severe neutropenia, antemortem accumulations of bacteria may occur with little or no reaction *B. welchii* invasion after death or even terminally prior to death is characterized by the presence not only of the large bacilli but of the spaces from the gas generated by the bacteria (plate 338). Monilial infection (plate 338) is particularly common in cases treated with nitrogen mustards, and may occur antemortem without appreciable inflammatory reaction (plate 338).

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*(Italicized page numbers refer to plates)*